Head and neck cancer in elderly patients

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Are there clinical variables to help guide the choice of treatment?

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General introduction

Epidemiology:

Incidence

In head and neck cancer the oral cavity, larynx and pharynx are the most common sites. There were respectively 1008, 753 and 674 new cases reported in the Netherlands in 2011. Other localizations of head and neck cancer include lip, salivary glands and (para) nasal sinuses, with a combined total of 535 new cases in 2011 in the Netherlands.

To compare incidences between regions usually the incidence is standardized for age, and shown in numbers of new cases per 100.000 (World Standardized Rate (WSR)). The WSR of head and neck cancer (lip, oral cavity, pharynx and larynx) was 8.96 per 100.000 in 2011 in the Netherlands (http://cijfersoverkanker.nl/), and 9.2 per 100.000 worldwide in 2008(Ferlay et al., 2010), these incidences have remained stable over the last decade.

Age

The definition of elderly patients is ambiguous, and diverse cut-off points are used to define old patients. The National Institute on Aging classified elderly patients into three groups: young old (aged 65-75 years), old (aged 75-85) and oldest old (aged 85 years and over).(*Website of the National Institute on Ageing*.) Most studies however define elderly patients aged 70 years and over.(Barzan et al., 1990; Bernardi et al., 2005; Derks, de Leeuw, Hordijk, & Winnubst, 2005; Kowalski, Alcantara, Magrin, & Parise Junior, 1994; Milet et al., 2010; Sanabria et al., 2008) There is an incremental increase of elderly people in the Netherlands, with a subsequently rising number of head and neck malignancies (Figure 1a). However, this increase does not translate into a rise number per 100.000 per age group in the Netherlands as shown in Figure 1b.

A more recent trend to define “elderly patients” is not by chronological age, but rather by biological age, where emphasis is laid on frailty of these patients. Schuurmans et al. defined frailty as ‘a loss of resources in several domains of functioning, which lead to a declining reserve capacity for dealing with stressors’.(Schuurmans, Steverink, Lindenberg, Frieswijk, & Slaets, 2004) A widely used multidisciplinary examination of elderly patient is the comprehensive geriatric assessment (CGA), evaluating functional status, cognition, psychological status, social support, nutritional status, co-morbidity and review of medications. However this assessment is time, money and energy consuming for both health-care provider and patient, therefore several, better obtainable screening tools were developed.(Hamaker et al., 2012; Kellen et al., 2010) These screening tools highlight different domains of functioning in a limited number of

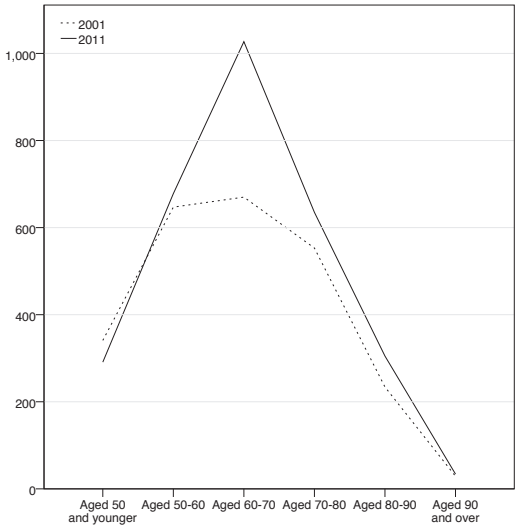

Figure 1a. Difference in incidence of head and neck cancer between 2001 and 2011 per age group

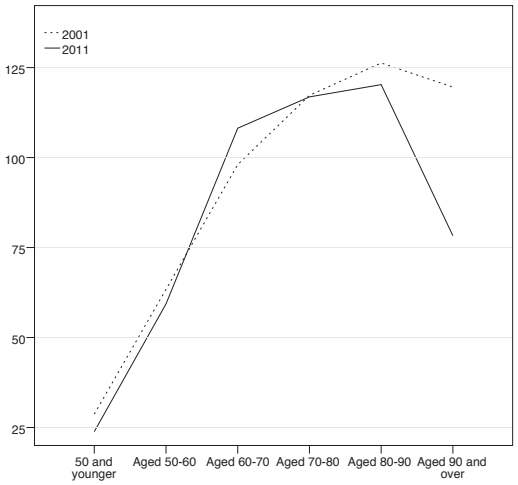

Figure 1b. Incidence per 100.000 per age group in 2001 and 2011

questions. The Groningen Frailty Index is an example of such a screenings tool with 15 questions divided over several domains of functioning.

Treatment of head and neck malignancy

The choice of treatment modality in head and neck cancer is rather complex and requires a multi-disciplinary approach, especially in elderly patients. The cornerstone of head and neck cancer treatment is surgery and (chemo)radiotherapy, very often in combination.

Surgery

Surgical resection can range from minimal invasive resection of the tumor, to large mutilating interventions requiring reconstructions with local or distant flaps.

A study of Derks et al.(Derks et al., 2005) showed that 64% of patient aged 80 years and over did not receive standard treatment, 31% of these patients were denied for surgery or received only limited surgery. Although comorbidity is thought to be a factor in the decision making process to discard elderly patients from treatment with extensive surgery; personal opinions of the doctor and the patient about tolerance of the treatment may also play a role.(Derks, de Leeuw, & Hordijk, 2005)

Because of the advances in pre-, peri-, and postoperative techniques and a shift of the paradigm towards standard treatment of elderly patients, increasingly more surgery is applied in elderly patients.

Radiotherapy

Radiotherapy is very often the chosen primary treatment of head and neck cancer with curative intention. This treatment has the advantage of preserving important organs, however function cannot always be preserved. Radiotherapy can also be applied post-operatively if certain tumor factors (e.g. extranodal tumor growth, not clear or close margins, etc.) indicate aggressive treatment or, when curation is not possible, in a palliative setting. Tolerance and the effect of radiotherapy in the elderly population are found not to be different to younger counterparts,(Mitsuhashi et al., 1999; T. Pignon, Horiot, Van den Bogaert, Van Glabbeke, & Scalliet, 1996) therefore this treatment can also be safely applied.

Chemoradiotherapy and other additional therapies

A large meta-analysis showed that the addition of chemotherapy to radiotherapy is not beneficial for patient of advanced age with head and neck cancer.(J. P. Pignon, le Maitre, Maillard, Bourhis, & MACH-NC Collaborative Group, 2009) No prolonged overall survival in elderly patient was seen in this meta-analysis using chemotherapy in addition to radiotherapy, possibly due to increased non-cancer related death in elderly, and higher toxicity of the chemotherapy in combination with more comorbidities. Furthermore no differences were seen in event-free survival between young and elderly patients. (J. P. Pignon et al., 2009)

More recent advances in treatment with targeted therapies like cetuximab, also show no additional effect on survival in elderly patient.(Bonner et al., 2010)
However, elderly patients are very often excluded from studies with experimental, non-standard treatment therefore it is simply not known if the aged population benefit from additional treatment.(Derks et al., 2005)

Clinical aspects

Comorbidity and elderly

The existence of one or more diseases in addition to the primary disease is described as co-morbidity. Previous studies show that these comorbid ailments increase the number and severity of complications during or after treatment(Borggreven et al., 2003; Ferrier, Spuesens, Le Cessie, & Baatenburg de Jong, 2005) and a shortens survival(Datema, Ferrier, van der Schroeff, & Baatenburg de Jong, 2010; Piccirillo & Vlahiotis, 2006; Singh et al., 1998). With rising age comorbidity increases(Borggreven et al., 2003; Piccirillo et al., 2008; Suh et al., 2004) both numerically and in severity, however it is unclear whether

Table 1. A selected number of specific comorbidities of the 12 different organ system in the Adult Comobidity Evaluation 27 (ACE-27) index. The complete form can be found on http://oto2.wustl.edu/clinepi/calc.html

Organ system (number of different ailments)	Selection of cogent comorbid ailment related to organ system	Specific Comorbidities (by Grade)		
		Grade 1: Mild Decompensation	Grade 2: Moderate Decompensation	Grade 3: Severe Decompensation
	Myocardial Infarct	Old MI by ECG only, age undetermined	MI > 6 months ago	MI ≤ 6 months ago
Respiratory System (1)	Respiratory disease	FEV1 (66%-80%)	FEV1 (51%-65%)	FEV1 (< 50%)
Gastrointestinal System (3)	Hepatic	Chronic hepatitis or cirrhosis without portal hypertension	Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	Portal hypertension and/ or esophageal bleeding ≤ 6 months ago (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)
Renal System (1)	End-Stage Renal Disease	Chronic Renal Insufficiency with creatinine 2-3 mg%	Chronic Renal Insufficiency with creatinine > 3 mg%	Creatinine > 3 mg% with multi-organ failure, shock, or sepsis
Endocrine System (1)	Diabetes Mellitus	AODM controlled by oral agents only	IDDM without complications	Diabetes causing end-organ failure including
Neurological system (4)	Stroke	Stroke with no residual	Old stroke with neurologic residual	Acute stroke with significant neurologic deficit
Psychiatric (1)	Mental Illness	Major depression or bipolar disorder controlled with medication	Major depression or bipolar disorder uncontrolled	Recent suicidal attempt
Rheumatologic (1)	Rheumatologic Disease	Connective Tissue Disorder on NSAIDS or no treatment	Connective Tissue Disorder on steroids or immunosuppressant medications	Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)
Immunological System (1)	AIDS	HIV+ w/o h/o AIDS defining illness CD4+ > 200/µL	HIV+ with h/o defining illness CD4+ < 200/µL	Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)
Malignancy (3)	Solid Tumor Including Melanoma	Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago	Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	Uncontrolled cancer
Substance Abuse (2)	Alcohol	H/o alcohol abuse but not presently drinking	Active alcohol abuse with social, behavioral, or medical complications	Delirium tremens
Body Weight (1)	Obesity		Morbid (i.e., BMI ≥ 38)	

Abbreviations: MI (Myocardial Infarction); FEV1 (Forced expiratory volume in 1 second), AODM (Adult-onset diabetes mellitus); IDDM (Insulin-dependent diabetes mellitus); NSAIDS (Non-steroidal anti-inflammatory drugs); CNS (Central nervous system); AIDS (Acquired immune deficiency syndrome); HIV (Human immunodeficiency virus); BMI (Body mass index)

Table 2. The Clavien-Dindo Classification of Surgical complications in the contracted form, the full scale can be found on http://www.surgicalcomplication.info/index-2.html

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management
Grade V	Death of a patient

this higher incidence of comorbidity in elderly results in more complications.(Beausang et al., 2003; Borggreven et al., 2003; Tsai et al., 2012) Several tools were created to evaluate comorbidity. The American Society of Anesthesiologist (ASA)(Saklad, 1941) classification is used often in clinical settings, however this classification is subject to a wide inter-observer variability, and therefore not readily applicable in research. The Charlson Comorbidity Index (CCI)(Singh et al., 1997) is regularly used in research on comorbidity in head and neck cancer, but does not take severity of comorbidity into account. A more comprehensive, widely used and validated tool in head and neck oncology research is the Adult Comorbidity Evaluation index 27 (ACE 27).(Piccirillo, Tierney, Costas, Grove, & Spitznagel, 2004) This index contains 26 items divided over 12 different organ systems, ultimately one comorbidity (severity) score is provided, dividing comorbidity into no, mild, moderate and severe comorbidity.

Complications and elderly

The occurrence of complications after treatment in elderly is analyzed only in retrospective studies, and mostly focuses on single treatment complications.(Boruk, Chernobilsky, Rosenfeld, & Har-El, 2005; Clayman, Eicher, Sicard, Razmpa, & Goepfert, 1998; Kowalski et al., 1994; Milet et al., 2010; Sarini et al., 2001) Most studies show that complications are not predicted by chronological age but scarce data is available whether patients received standard or non-standard treatment.(Boruk et al., 2005; Clayman et al., 1998; Kowalski et al., 1994; Milet et al., 2010; Sarini et al., 2001) Another problem with previous literature is the lack of an easy and standardized way of classifying complications, thus previous literature is hard to compare. A very complicated and comprehensive method to classify complications is the Common Terminology Criteria for Adverse Events (CTCAE). Although this is very complete and applicable for different treatments, this method is not suitable for retrospective research and possibly even too complicated for prospective studies. Recently, a new classification of surgical

complications was created, the Clavien-Dindo classification (CDC) system. (Clavien et al., 2009; Dindo, Demartines, & Clavien, 2004) This classification is also suitable for scoring complications after head and neck surgery but not yet widely applied. (Perisanidis et al., 2012) This classification is based on the treatment needed to treat a complication, rather than on the complication itself. This characteristic of the CDC makes is suitable and reliable for retrospective studies, as in clinical charts treatment is usually better registered than observations.

Survival and elderly

The life expectancy is obviously lower as age progresses, therefore this factor should always be accounted for when treating elderly patients. However the question arises if head and neck cancer differently affect the survival of elderly patients than the younger population. A large study by Colonna et al. showed that elderly patients treated for head and neck have a higher risk of death in the first year after treatment. One possible explanation is the higher occurrence of postoperative complications, but one can also speculate the higher percentage of patients treated by suboptimal, non-standard treatment in the elderly group.(Colonna, Bossard, Remontet, Grosclaude, & FRANCIM Network, 2010) Compared to younger patients, some studies found that elderly patients have a shorter life expectancy regarding overall survival over a longer period of time. (Boje et al., 2013; Datema et al., 2010) However literature is not consistent, and other studies found no difference in survival of head and neck cancer patients.(Bhattacharyya, 2003; van der Schroeff, Derks, Hordijk, & de Leeuw, 2007).

Aims of the present thesis

The number of elderly patients is rising, and expected to keep rising in the future. Clinicians are often faced with the dilemma which treatment is best suitable for the individual patient in terms of toxicity of treatments and the subsequent survival. Therefore, this thesis aims to study the following questions:

- Are there differences in the complication pattern of different treatment modalities in head and neck cancer patients?
- Is it possible to perform surgery safely in elderly head and neck cancer patients?
- Are elderly patient suitable for complex reconstruction of defects after head and neck surgery?
- Is it possible to predict postoperative complications using factors known before treatment? Are there differences in this prediction between different age groups?

Complication and survival of young and elderly after surgery and radiotherapy

2.1 The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer

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Oral oncology. 2011;47:56-61

Introduction

With the prolonged life expectancy among cancer patients in the Western world, special attention should be paid in the treatment of the ageing population. There is no real consensus with regard to the proper age definition of geriatric patients. The most accepted classification comes from the National Institute on Ageing, where patients between 65-74 are defined as “young old”, 75-84 as “older old” and 85 and older as “oldest old”.(*Website of the National Institute on Ageing*.) Some studies emphasize the importance of biological and not chronological age.(Bernardi et al., 2005; Genden et al., 2005; Sanders, Blom, Singer, & Hamaker, 1990) Although age is not an independent negative prognostic factor in head and neck cancer treatment(Barzan et al., 1990; Leon et al., 1998), non-standard treatment is more frequently applied in elderly patients(Derks, de Leeuw, Hordijk, & Winnubst, 2004; Derks et al., 2005; Hirano & Mori, 1998; Jones, Husband, & Rowley, 1998; Kowalski et al., 1994; Sarini et al., 2001). Single modality treatment is more likely to be chosen, extended surgery is less frequently performed and there is a paradigm to prefer radiation therapy instead of surgical intervention. Some studies found that pre-treatment co-morbidity is significantly associated with treatment-related complications.(Borggreven et al., 2003; Datema et al., 2010; Ferrier et al., 2005) In general, elderly patients have higher rates of co-morbidity. Therefore, most of the studies propose careful pre-treatment evaluation of elderly patients.(Clayman et al., 1998; Derks et al., 2005; Genden et al., 2005) Interestingly, despite of the positive correlation between age and co-morbidity and between co-morbidity and complication rate, conflicting data exist on the relationship between age and complication rate. (Borggreven et al., 2003; Derks et al., 2005)

Laryngeal squamous cell carcinoma is the most common head and neck malignancy in elderly patients (excluding thyroid)(Bernardi et al., 2005; Cooper et al., 2009) and represents a relatively homogenous group. The two major aims of the present study were to test the hypothesis that treatment-related complications in elderly patients with laryngeal cancer are related to co-morbidity and to test as to whether the incidence and patterns of treatment-related side effects differ from the younger population. It is also intended to explore possible outcome differences among treatment modalities in order to be able to provide more accurate information for choosing the most appropriate treatment option.

Materials and methods

Patients

In this retrospective cohort study, medical charts of all patients with laryngeal squamous cell carcinoma, diagnosed at the University Medical Center Groningen, the Netherlands, between 1997 and 2007 were analyzed retrospectively. The study cohort was composed of patients with supraglottic and glottic cancer, ≥75 years of age at the time of diagnosis. Patients with subglottic cancers were excluded because of the different nature of the tumor and the small number of patients in this specific subset. Patients treated with palliative intention were also excluded, because the purpose of the study was to determine the risk on treatment-related side effects of standard curative treatment in elderly patients and not to compare the process of decision-making in different age groups. All tumor histology other than squamous cell cancer were also excluded.
The control group consisted of patients younger than 65 years of age with similar tumor characteristics as in the observational group. “Young old” patients aged between 65 and 75 were excluded in order to highlight the differences between young and old patients.

Patients’ data

Primary data collection from medical records (patients’ clinical electronic database and clinical chart) included age, sex, tumor site, stage, treatment modality, treatment-related complications, loco-regional recurrence and overall survival time in months. Co-morbidities were graded according to the Adult Comorbidity Evaluation 27 index (ACE-27). Calculations were made using the algorithms as publishes on the website of the Department of Otolaryngology and Head and Neck Surgery of the Washington University School of Medicine St. Louis, Missouri, USA.(Piccirillo,) ACE-27 divides comorbidity into four groups; no (0), mild (1), moderate (2) and severe decompensation (3).

A simple rating system was used and classified the complications in three groups: (0) no complications; (1) moderate complications, which did not required inpatient admission or further surgical interventions, and; (2) severe complications, when patients had to be re-operated upon or when their clinical status required or significantly prolonged hospitalization. Only early complications, during or shortly after treatment (within 3 months) were reviewed in this study. One- and six-month death rates, as well as recurrences were recorded.

Statistic analysis

Statistical analysis was carried out in SPSS 16.0 for Windows. To determine statistical

significance in the cohort and the reference controls concerning complications and one-month and six months overall survival, the Pearson chi quadrate test was used. Multivariate logistic regression analysis was performed in order to discover whether treatment option, co-morbidity, stage or age affect the treatment-related complications. Levels of significance were considered as follows: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Results

Patients' characteristics are summarized in Table 1. No significant differences were noted between the two age groups regarding tumor stages, although the incidence of glottic tumors in the elderly group was slightly higher, i.e., 83% vs. 68% in the younger group. There were no significant differences in the primary treatment modalities applied in older and younger patients, although total laryngectomy was less frequently chosen in the elderly population (8 % vs. 14 % in the young group). There was no significant difference in loco-regional recurrence rate.

ACE-27 grade could be assigned in 411 out of the 412 included patients. In the entire patient population, most patients (69%) had no or mild co-morbid conditions (ACE-27 grades 0 and 1). Moderate co-morbidity (ACE-27 grade 2) occurred in 27% of patients and only 4% of the patients had severe decompensation (ACE-27 grade 3). In the elderly group significantly more co-morbidity was observed ($p<0.001$) than in the younger group (Figure 1a). The percentage of patient with no comorbidity was 46% in the young and 20% in the elderly group, while the proportion of patients with moderate

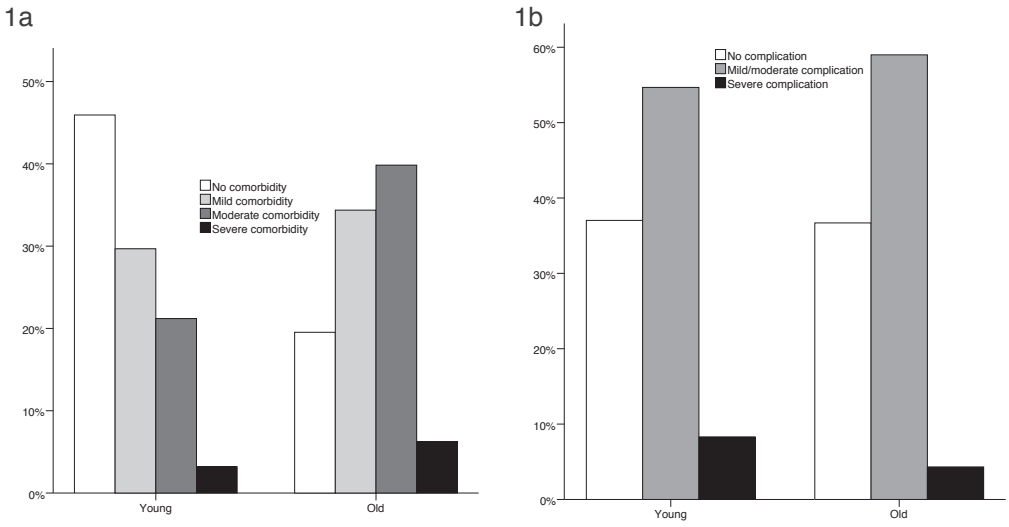

Figure 1. Co-morbidity and complication Figure 1a. Bar chart shows the percentage of co-morbidity in young and old patients. Figure 1b. Bar chart shows the percentage of post-treatment complications in young and old patients

and severe co-morbidity was almost twice as high in the elderly group.

No significant difference was found in the rate of complications between the two age groups (Figure 1b). Severe treatment-related complications occurred in only 7% of the whole patient population, while in most cases, both in the younger and elderly group, only mild or moderate complications appeared in most cases (respectively 55% and 63%). In the analysis of the association between comorbidity and complications (Figure 2) severe co-morbidity was discarded because of the small number of patient with severe co-morbidity. In the total group of patients, co-morbidity was a significant (p=0.042) predictor of complications (Figure 2a). This association was also found in younger group (Figure 2b). However, in the elderly group, co-morbidity was not a significant predictor of complications, (Figure 2c).

We have analyzed the complication rate in the different treatment groups (Figure 3). Complications after endoscopic CO_2-laser treatment were significantly less than after radiotherapy or total laryngectomy in both elderly and younger groups. After total laryngectomy, complications were less frequently observed in the younger group (no complication: 39%) than in the elderly group (18%), but complications were more severe in the younger group. Radiotherapy was associated with mild to moderate complications in both age groups. The one and six months' survival of our patients were registered (Table 2). Significantly more patients died in the old group six months after treatment (p=0.021), the one month survival was also lower in the elderly group, but this was not

Table 1. Characteristics of included patients

	<65 y	≥75 y	P value
N	283	129	
Age (years)			
Mean (range)	55 (33-64)	79 (75-97)	
Sex			
Male	229 (81)	113 (88)	0.094
Female	54 (19)	16 (12)	
Stage (%)			
0 (T_{cis})	14 (5)	2 (2)	
I	114 (40)	61 (47)	0.057
II	69 (24)	30 (23)	
III	22 (8)	17 (13)	
IV	64 (23)	19 (15)	
Site			
Supraglottic	92 (32)	22 (17)	0.001
Glottic	191 (68)	107 (83)	
Treatment modality			
CO2 laser	60 (21)	36 (28)	0.153
Radiotherapy	184 (65)	82 (64)	
Laryngectomy	39 (14)	11 (8)	
Recurrence			
No recurrence	171 (60)	84 (65)	0.385
Recurrence	111 (40)	45 (35)	

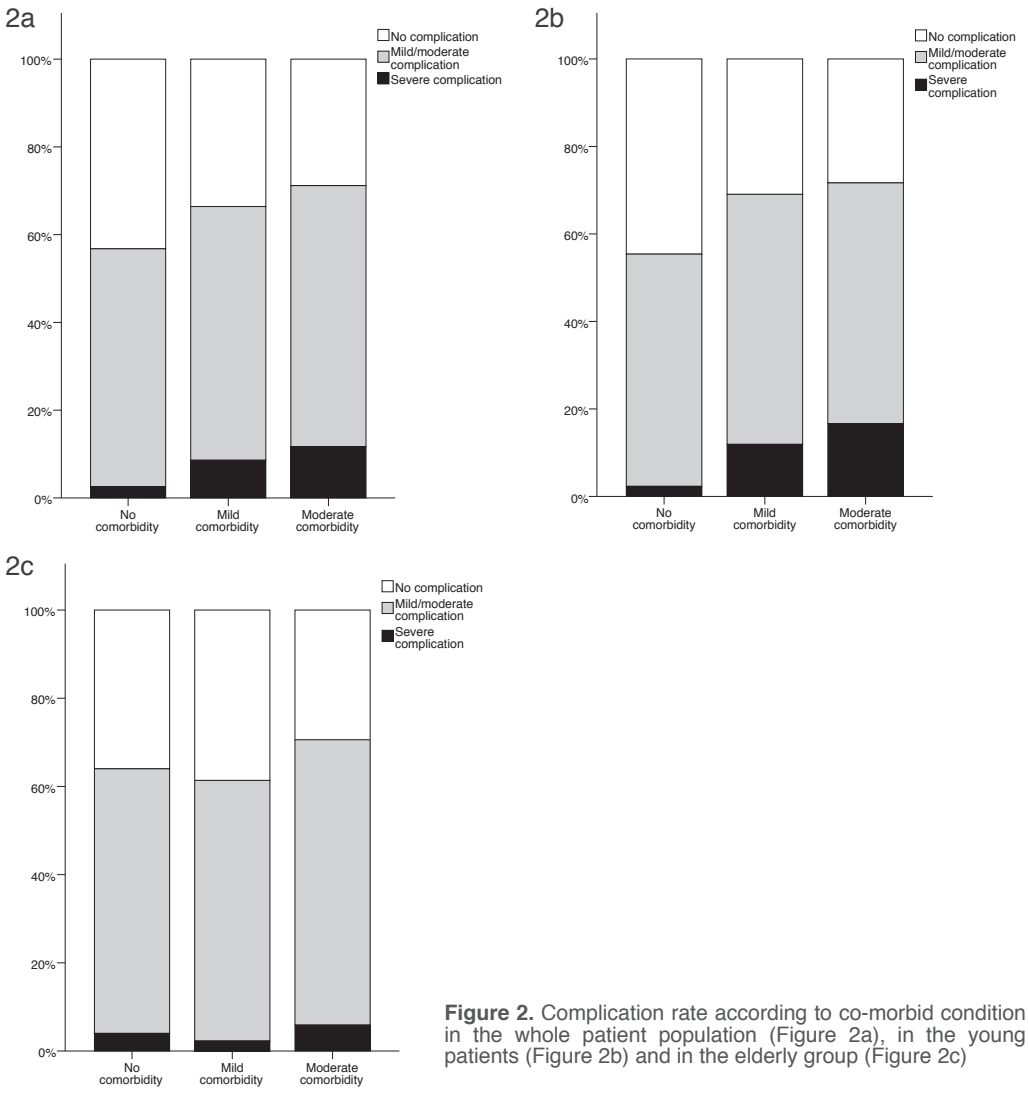

Figure 2. Complication rate according to co-morbid condition in the whole patient population (Figure 2a), in the young patients (Figure 2b) and in the elderly group (Figure 2c)

statistically significant (p=0.061). No patients died within the one month interval after total laryngectomy, however three patients in the young group (8%) and one patient in the old group (9.1%) died within six months (not significant).

However, among patients treated with radiotherapy, a significant difference (p=0.003) was found in six months survival between younger and elderly patients. In the group of elderly patients, 12 (15%) died while in the younger age group only eight (4.3%) patients died within six months after radiotherapy. Multivariate analysis (Table 3) has been performed in the whole population (A), in the young (B) and elderly group (C). This analysis showed that co-morbidity and age at diagnosis were not associated

with treatment-related complications rate in any groups. However, tumor stage was a significant predictor of complication in the whole study population and in both age subgroups. Radiation therapy vs. total laryngectomy has also been a significant factor that affected the complication rate in both the young and elderly groups, although in the elderly group the significance was weaker (p=0.028).

Discussion

The importance of co-morbidity in the management of head and neck cancer is evident. In a recent paper by Paleri et al.(Paleri et al., 2010), all important literature data was collected on the influence of co-morbidity on head and neck cancer outcome. On basis of reviewing the literature the authors raise the possibility that co-morbidity could be incorporated into the future versions of the TNM classification. Our results confirm the higher incidence of co-morbidity in the elderly population. The opposite trend in the severity of co-morbidity is striking (Fig. 1a), despite of the fact that all palliatively treated patients were excluded. The number of patients treated palliatively (therefore excluded from our study) has been significantly higher in the elderly group (7% vs. 2%). The most frequently mentioned reason to decide for palliative rather than curative treatment was the presence of co-morbid conditions or the wish of the patient.

It is well known that the complication rate increases with the incidence of co-morbidity. (Derks et al., 2005; Sanabria et al., 2008) However, according to the literature(Clayman et al., 1998; Gall, Sessions, & Ogura, 1977; McGuirt & Davis, 1995; T. Pignon et al., 1996) age is not related to complication rate. Our results are in line with these studies; the pattern of post-treatment complication was the same in the young and elderly population (Fig. 1b); in both groups most of the patients had mild and moderate co-morbidities but rarely severe. In our study a clear relationship has been found between co-morbidity and complication rate in the whole population and especially in the younger patients (Fig. 2a and b). This relationship was not present in the elderly population (Fig

Table 2. One- and six-month death rate in old and young patients after radiotherapy and total laryngectomy. The percentage noted with the number of patients represents the percentage of deceased patient within the age group of the treatment modality

Treatment modality	Age group	Death within one month	Death within six months
Radio therapy	Young	2 (1.1%)	8 (4.3%)
	Old	4 (4.9%)	12 (14.6%) **
Total laryngectomy	Young	0	3 (7.7%)
	Old	0	1 (9.1%)

** indicates the level of significance (p<0.01)

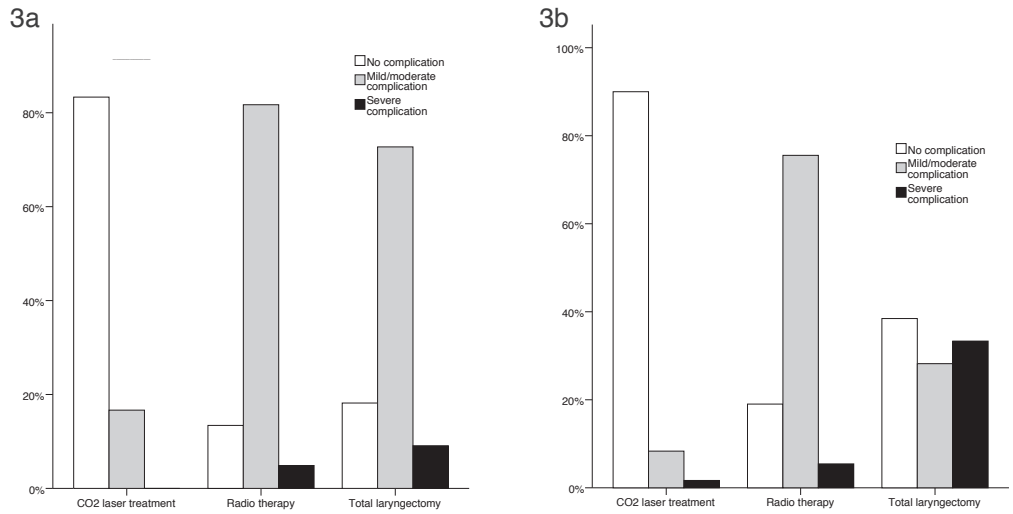

Figure 3. Distribution of complication severity after different treatment modalities in old (Figure 3a) and in young (Figure 3b) patients

2c), which is difficult to explain. Multivariate analysis did not show any significant effect of co-morbidity in either age groups (Table 3). One of the main reasons to perform this study was our controversial experiences with unpredictable patterns of post-treatment complications in elderly head and neck cancer patients. These results underline the difficulty to predict the postoperative course in elderly and further emphasize the importance of careful pre-treatment evaluation of elderly patients. Currently, at our institution, a well-experienced senior ENT anesthesiologists and geriatrician perform an extra preoperative check-up in patients with advanced age regardless of co-morbidity. However, before radiation therapy such a careful evaluation is not standard, which could be considered based on these results.

Minimally invasive endolaryngeal laser surgery has found to have low rate of mild and absence of severe complications in both old and young patients. This is not surprising. Our inclusion of T1a glottic laryngeal carcinoma for endolaryngeal CO2-laser surgery is done according to the Dutch treatment protocol. Only tumors limited to the free rim of the vocal cord and not including the anterior commissure are considered to be candidates for laser surgery. Radiation therapy had relatively high complication rates in both age groups, but usually these conditions did not necessitate hospitalization, treatment interruption or interventions. No significant difference was detected in the occurrence and severity of complications between young and elderly patients. Similar results were found by other investigators.(Allal, Maire, Becker, & Dulguerov, 2000; Chin, Fisher, Smee, & Barton, 1995; Schofield, Sykes, Slevin, & Rashid, 2003) We experienced controversial outcome data with total laryngectomy (Figures 3a and 3b).

Table 3. Multivariate analysis of factors affecting treatment-related complication in all patients (A), in the younger group (B) and in the elderly group (C)

A.

Multivariate analysis of factors affecting treatment-related complication in all patients			
Variable	**Odds Ratio (95% confidence interval)**	**P value**	**Level of significance**
Treatment (RT/TLE)	10.322 (4.546-30.043)	<0.001	***
Comorbidity	1.264 (0.927-1.723)	0.139	ns
Stage	1.982 (1.384-1.838)	<0.001	***
Age at diagnose	1.009 (0.987-1.032)	0.411	ns

B.

Multivariate analysis of factors affecting treatment-related complication in young patients			
Variable	**Odds Ratio (95% confidence interval)**	**P value**	**Level of significance**
Treatment (RT/TLE)	7.822 (2.462-24.852)	<0.001	***
Comorbidity	1.455 (0.999-2.118)	0.051	ns
Stage	1.604 (1.070-2.404)	0.022	*
Age at diagnose	0.972 (0.927-1.019)	0.236	ns

C.

Multivariate analysis of factors affecting treatment-related complication in elderly patients			
Variable	**Odds Ratio (95% confidence interval)**	**P value**	**Level of significance**
Treatment (RT/TLE)	21.312 (1.391-326.630)	0.028	*
Comorbidity	0.907 (0.483-1.703)	0.761	ns
Stage	3.402 (1.506-7.681)	0.003	**
Age at diagnose	1.165 (0.989-1.372)	0.068	ns

Young patients had significantly lower complication rates (almost 40 % without any complication vs. almost 20% in elderly), but if a complication occurred, it was more often severe in the younger group. These data can be explained by more factors; (1) there has been a better patient selection made in the elderly group, and therefore more patients were excluded and palliatively treated, (2) older patients are preoperatively more thoroughly checked-up than younger ones. Our findings are in conjunction with previous studies about major head and neck interventions in elderly patients.(Clayman et al., 1998; Kowalski et al., 1994; McGuirt, Loevy, McCabe, & Krause, 1977) The one- and six-month overall survival rates of the young and old patients have been compared according to treatment modality. In the literature no differences were found in survival outcome between young and elderly patients after both major treatment modalities (surgery and radiotherapy).(Clayman et al., 1998; T. Pignon et al., 1996) Our results of the one month survival data are in line with these studies, but in the present study significantly more elderly patients died within six months after completion of treatment (Table 2). The fact that more young patients died after major surgery suggests the better patient selection in the elderly group. In patients treated with radiotherapy the one-month post-survival was not statistically different. The surprisingly favorable results

of total laryngectomy in the elderly group have already been discussed. It is most likely, that these favorable results are due to the fact that only the very fit elderly patients were selected for TLE instead of primary non-surgical treatment, e.g., patients with increased co-morbidities were not selected for TLE. These results also underline the value of careful pre-treatment evaluation of elderly patients, regardless of treatment of choice.

In conclusion, our study provides further ev idence that elderly laryngeal cancer patients should be treated according to the best medical practice standards and chronological age itself is no reason to treat elderly patients differently. It has to be added that we have only analyzed the effect of surgery and radiotherapy on elderly patient and not all treatment options (like chemotherapy or Cetuximab). According to a recent meta-analysis(J. P. Pignon et al., 2009) chemotherapy has significant less benefit on older head and neck cancer patients and similarly decreased effect of Cetuximab has been found in the 65+ population.(Bonner et al., 2010) A relationship between age and co-morbidity was found, but no correlation between age and complication rate. The lack of a correlation between co-morbidity and complications in elderly makes it difficult to forecast postoperative problems. Our results suggest that it is also difficult to predict the prognosis in the elderly since no relation has been found between stage and recurrence rate in the 75+ population. These results emphasize the importance of thorough pre-treatment evaluation of elderly laryngeal cancer patients.

Complication and survival of young and elderly after surgery and radiotherapy

2.2 Co-morbidity and treatment outcomes of elderly pharyngeal cancer patients: A matched control study

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Introduction

In the Netherlands, the incidence of pharyngeal cancer is rising from 2.5 ESR (European Standardized Rate) per 100,000 in 1993 to 3.4 ESR per 100,000 in 2008 (www.ikcnet.nl). This progression correlates with an increase in alcohol consumption. The incidence of pharyngeal cancer is highest between 45 and 74 years of age (80%), while 14% of all new cancer cases occur among those of 75+ years of age. In general, overall survival (OS) of pharyngeal cancer patients is poor. According to the Dutch Cancer Registry, the 5-year OS of hypopharyngeal cancer is 31%. Outcome is even more disappointing in the 75+ population, in which the 5-year OS is only 18%. OS is particularly associated with loco-regional tumor extension, ranging from 72% after 5 years in stage I to only 20% in stage IV disease. Prognosis among patients with oropharyngeal cancer is not much better. In this subset, the 5-year OS is 41%, decreasing to 30% in the elderly population and also depending on stage (www.ikcnet.nl).

In the Western world, the proportion of elderly people dramatically increased in the last decades, which also translated into an increase in elderly patients with head and neck cancer. These elderly patients generally suffer from markedly more co-morbid conditions, which are associated with higher rates of treatment-related side effects and poorer prognosis.(Blackwell, Azizzadeh, Ayala, & Rawnsley, 2002; Borggreven et al., 2003; Datema et al., 2010; de Cassia Braga Ribeiro, Kowalski, & Latorre Mdo, 2003; Homma et al., 2010; Paleri et al., 2010; Reid et al., 2001) Several studies emphasized the importance of thorough pre-treatment evaluation in particular in elderly patients. (Bernardi et al., 2005; Genden et al., 2005; Peters, van der Laan et al., 2011) Although, several authors stated that elderly patients should be treated similarly to the younger ones(Derks et al., 2005; Lalami, de Castro, Bernard-Marty, & Awada, 2009; Peters, van der Laan et al., 2011; Reizenstein et al., 2010; Sesterhenn, Teymoortash, Folz, & Werner, 2005), the question arises as to whether intensified and often mutilating treatment approaches are most suited for patients with an expected 5 years survival rate of less than 20%. In order to add useful information to this interesting dilemma, we compared data of elderly patients with oropharyngeal and hypopharyngeal cancer to that of younger patients with regard to their co-morbid status, treatment-related complication and OS rate. The secondary objective of this study was to explore the factors associated with complication rates and OS among elderly patients with pharyngeal cancer.

Patients and methods

Patients

All patients with pharyngeal cancer diagnosed at the University Medical Center Groningen, Groningen, the Netherlands, between 1997 and 2007 were included in this retrospective cohort study. The study population consisted of patients 75 years of age at the time of diagnosis of oropharyngeal and hypopharyngeal squamous cell carcinoma (SSC). Patients with nasopharyngeal cancer and/or patients treated with curative chemoradiation were excluded. Each included patient was matched with two patients of <65 years of age at diagnosis by tumor site, tumor stage, treatment intention and year of treatment.

Patients' data

Data was obtained from patients' clinical electronic database and clinical chart. Primary data included age, tumor site, stage, treatment modality, treatment-related complications and overall survival time after treatment in months. Pre-treatment comorbidity was classified according to the web based Adult Comorbidity Evaluation 27 (ACE 27) index calculator (http://oto2.wustl.edu/clinepi/calc.html). The ACE 27 index divides comorbidity into three severity categories; mild decompensation, moderate decompensation, and severe decompensation. The ACE-27 index is a comorbidity classification system based on the Kaplan–Feinstein Comorbidity index(Kaplan & Feinstein, 1974) and was modified by Bang et al.('Bang, 'Piccirillo, 'Littenberg', & Johnston, 2000) In the current study, comorbidity data have been calculated with and without item 24 (alcohol consumption data) of the ACE-27 analysis. Alcohol abuse is a known etiologic factor of pharyngeal cancer; therefore the high incidence of alcohol abuse is predictable. Therefore, it was also aimed to calculate the comorbidity without letting our data hampered by this item.

Classification of complications was scored as no complications, mild/moderate complications or severe complications as previously described(Peters, van der Laan et al., 2011), complemented with death (Table 1). This rating system is comparable with the classification of the Common Terminology Criteria for Adverse Events system (CTCAE version 4.02). However the retrospective nature of our study did not allow for the same detailed analysis of the CTCAE. Only complications that occurred within 3 months after treatment were included. In case of palliative treatment, the reason for this decision was also recorded and subdivided into four categories; patients' choice, tumor extension, age and poor general condition.

Statistic analysis

For the comparison of comorbidity and complications, and for the analysis of the reasons for palliative treatment, the chi-square test was used. To analyze the effect of age, stage, comorbidity and treatment modality on complications, multivariate logistic regression analysis was performed. For multivariate logistic regression, complications were divided into two groups; no/mild-moderate complications and severe/fatal complications. Separate analyses were conducted comparing individual comorbidities and stages.

Survival analysis was performed in two different ways. First, survival estimates were conducted using the method of Kaplan and Meier and compared with the log rank test. Survival was censored for patients who survived the 5-year follow up period. Survival times were calculated from the date of initializing treatment and were cut at 5 year. Second, to adjust for differences in age, survival times were adjusted for the median life expectancy of individuals in the general population with the same age and sex. Differences were tested using the log-rank test with left and right censoring and median life expectance, as time base. This median life expectancy was derived from gender specific reports provided by the Dutch Central Offices of Statistics (http://statline.cbs.

Table 1. Scoring complications in the present study and its comparison to other complication rating systems

Scoring used in present study		**Radiotherapy**		**CTCAE v4.0**	
0	No complication	0	No change over baseline	0	No complication
1	Mild/moderate complication (Complication not necessitating further inpatient admission or further surgical intervention)	1	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
		2	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
2	Severe complications (Complication necessitating re-operation or significantly prolonged hospitalization urged by clinical status)	3	Severe dysphagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring nasogastric feeding tube, intravenous fluids or hyperalimentation	3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
		4	Complete obstruction, ulceration, perforation, fistula	4	Life-threatening consequences; urgent intervention indicated.
3	Complication causing death	5	Causing death	5	Death related to AE

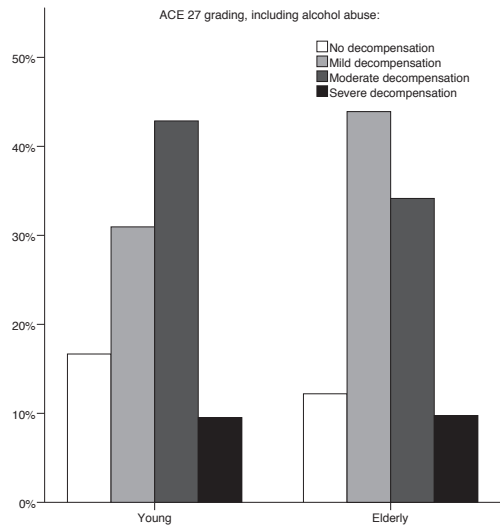


Figure 1a. Distribution of comorbidity, graded using ACE 27, over young and elderly pharyngeal cancer patients.

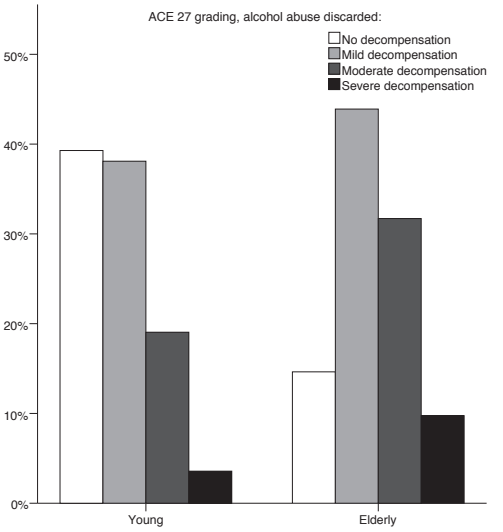


Figure 1b. Distribution of comorbidity, graded using ACE 27, over young and elderly pharyngeal cancer patients after discarding item 24 (alcohol abuse).

nl/StatWeb/). The time basis used in the adjusted graphs is negative life expectancy (-EXP). With life expectancy as a time basis, patients with the same life expectancy are compared with the data that is already corrected for age, sex and birth cohort. Patients with longer life expectancies belonged to the younger group of patients in this study. Significance of variables affecting survival was assessed using the log-rank test. Statistical analyses were executed using SPSS 15.0 and Microsoft Excel 2003 for windows.

Results

Demographics

The demographic and other pre-treatment variables of all included patients are described in Table 2. No significant differences were noted between the elderly and younger patients with regard to curative primary and secondary treatment modality. Radiotherapy was somewhat less frequently applied in elderly patients (59% vs. 65% in the younger group). Elderly patients more frequently received a secondary neck dissection and less often postoperative radiotherapy, but these differences were not significantly different.

Comorbidity

No significant differences in comorbidity were found between younger and elderly patients, scored according to the complete ACE-27 system. However, in younger

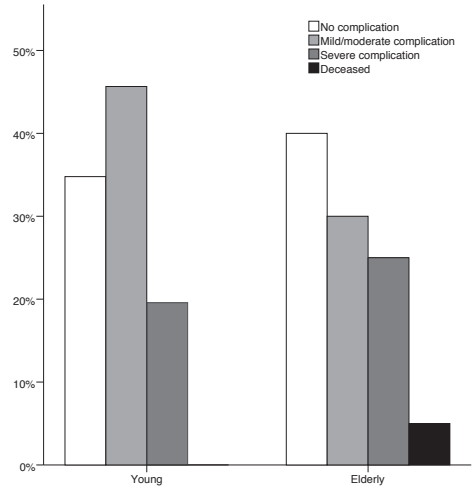


Figure 2. Distribution of complication after treatment in young and elderly pharyngeal cancer patients. Complication was subdivided over no complication, mild/moderate complication, severe complication and death.

patients less decompensation was observed (17% vs. 12 % in elderly). The most frequently observed severity of decompensation in elderly patients was mild (44%), whereas in younger patients moderate decompensation was most frequent (43%) (Fig. 1a). The relatively high percentage of moderate co-morbidity rate can be explained by the fact that alcohol abuse itself results in a moderate co-morbid classification in the

Table 2. Characteristics of included patients

	<65 y	≥75 y
N	84	42
Age (years)		
Mean (range)	53 (38-64)	80 (75-87)
Sex (%)		
Male	59 (70)	29 (69)
Female	25 (30)	13 (31)
Stage (%)		
I	4 (5)	3 (7)
II	10 (12)	4 (10)
III	1 (1)	3 (7)
IV	69 (82)	32 (76)
Site (%)		
Oropharynx	38 (45)	19 (45)
Hypopharynx	46 (55)	23 (55)
Treatment intention (%)		
Curative	46 (55)	22 (52)
Palliative	38 (45)	20 (48)
Primary treatment modality with curative intent (%)		
Minor surgery	1 (2)	3 (14)
Major surgery	15 (33)	6 (27)
Radiotherapy	30 (65)	13 (59)
Secondary treatment modality (%)		
Neck dissection	5 (6)	5 (11)
Radiotherapy	13 (16)	4 (9)

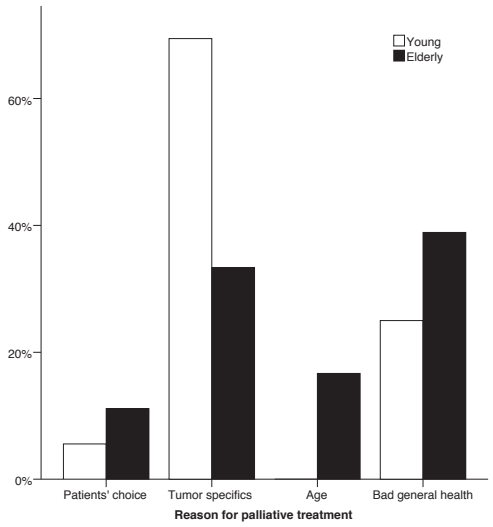


Figure 3. Distribution of young and elderly pharyngeal cancer patient according to reason for palliative treatment.

ACE-27 system. When alcohol abuse was discarded from the ACE-27 score (item 24.), a significant difference in comorbidity was found between young and elderly patients (p= 0.025) (Fig. 1b).

Complications

Severe complications were observed in 25% of the elderly patients and in 20% of the younger ones. Death within 3 months occurred only in one occasion (5%) in the elderly group, while such an event did not occur in the younger age group. The difference in occurrence of complications was not statistically significant (p = 0.330) (Fig. 2).

Multivariate analysis of factors affecting complications

No relation was found between comorbidity and treatment-related complications in the entire population, neither in young patients nor in elderly patients. In the multivariate analysis, only tumor stage was significantly associated with complications (p = 0.041), while age at diagnose was not. For other potential prognostic factors, including comorbidity and treatment modality, no significant associations were found with complications (Table 3).

Palliation

With respect to the reasons to decide for palliative treatment, no significant differences were noted regarding patients' choice and bad general health between young and elderly patients. However, in the elderly group, tumor extension was reason for the choice of palliative treatment in six patients (33%), while in young patients, this was the case in 25 (69%) of the cases, which was statistically significant (p = 0.003) (Fig. 3).

Table 3. Multivariate analysis of factors affecting treatment-related complication in all patients

Variable		Odds ratio (95% confidence interval)	P trend value
Age at diagnose		1.018 (0.976-1.062)	0.401
Stage	Stage I	1 (ref)	**0.041**
	Stage II	1.425 (0.180-11.264)	
	Stage III	3.576 (0.155-82.764)	
	Stage IV	5.839 (0.807-42.249)	
Comorbidity (ACE 27)	No decompensation	1 (ref)	0.921
	Mild decompensation	0.323 (0.062-1.686)	
	Moderate decompensation	0.748 (0.133- 4.187)	
	Severe decompensation	0.435 (0.041-4.614)	
Primary treatment modality	Major surgery	1 (ref)	
	Minor surgery	0.320 (0.018-5.611)	0.435
	Radiotherapy	0.860 (0.249-2.973)	0.812

Survival

The Kaplan–Meier survival estimates of patients with pharyngeal tumors (excluding those selected for palliative treatment) stratified by age group are shown in Fig. 4. Overall, survival in elderly patients (5 year survival was 9%) was significantly worse compared to that observed in young patients (5 year survival was 39%) ($p = 0.003$). In the univariate analysis, no significant association was found between comorbidity and overall survival (Fig. 5a). After adjusting for age, sex and birth cohort, (Fig. 5b) the study population was subdivided based on comorbidity. In both analyses, comorbidity was divided into the subgroups no/mild and moderate/severe co-morbid status. This analysis showed a significant ($p < 0.001$) decrease of survival with the increasing decompensation.

Discussion

In the present study, no different post-treatment complication rates between young and elderly patients were observed, despite of the higher incidence of pre-treatment co-morbid condition in elderly patients. In the multivariate analysis, the only factor that was significantly associated with the frequency of complications was tumor stage with a higher risk on complications with increasing stage. In addition, in the current study we did not find worse survival with higher levels of comorbidity in the unadjusted Kaplan–Meier estimates. However, when adjusted for life expectancy according to age, moderate-to-severe comorbidity was associated with worse survival expectancy. These findings stress the importance of adjusting the observed survival times for age when comparing survival between young and elderly patients. Statistically it is not correct to compare overall survival analysis rates of two different age groups with conventional Kaplan–Meier analysis. Using life expectancy calculations, the time before expected

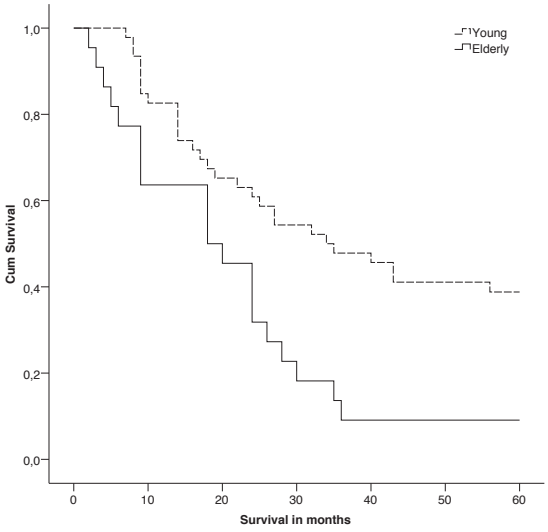
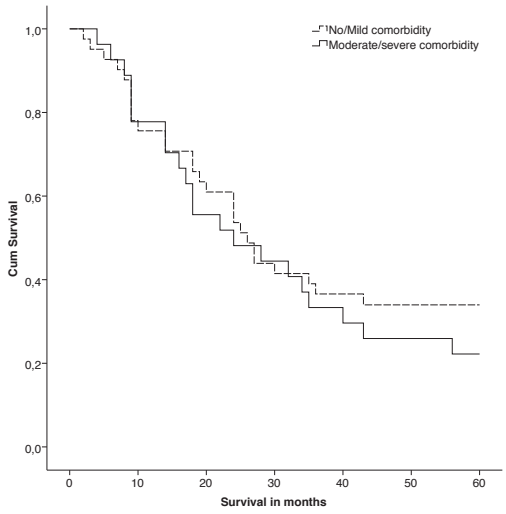


Figure 4. Kaplan–Meier estimates of overall survival, subdivided over young and elderly curative treated patients.

death is expressed and compared to the general population matched on age and sex, therefore excluding the effect of age and sex on survival. This approach of survival has not been yet used previously in the analysis of elderly head and neck cancer patients. Using life expectancy comparing two different age groups can therefore provide more accurate information than using the conventional Kaplan–Meier survival estimates.

It is evident from the literature that comorbidity increases with age.(Paleri et al., 2010) Using the ACE-27 comorbidity classification system, we could not confirm these findings. However, the algorithm of the ACE-27 scoring system includes excessive alcohol consumption, which is a well-known risk factor for pharyngeal cancer. In the current study, the percentage of elderly head and neck cancer patient currently abusing alcohol was significantly lower as observed among the young one, which has also been found in other studies.(Koch, Patel, Brennan, Boyle, & Sidransky, 1995) However, elderly patients frequently had a past history of alcohol abuse. In our study, this item was frequently scored positive for active alcohol abuse among younger patients. According to the ACE-27 system the co-morbid condition ‘‘falls’’ from grade 2 in case of ‘‘active alcohol abuse’’, to grade 1 in case of a ‘‘history of alcohol abuse but not presently drinking’’ (http://oto2.wustl.edu/clinepi/calc.html). In the present study, the high rate of grade 2 co-morbid condition in young patients was highly determined to active alcohol abuse. Indeed, when we re-calculated the co-morbidity data discarding alcohol abuse (item 24) a significantly lower ACE-comorbidity score was observed among the young age group. In most studies, no higher incidences of complications are found in elderly patients after surgery(Clayman et al., 1998; Kowalski et al., 1994; McGuirt et al., 1977)



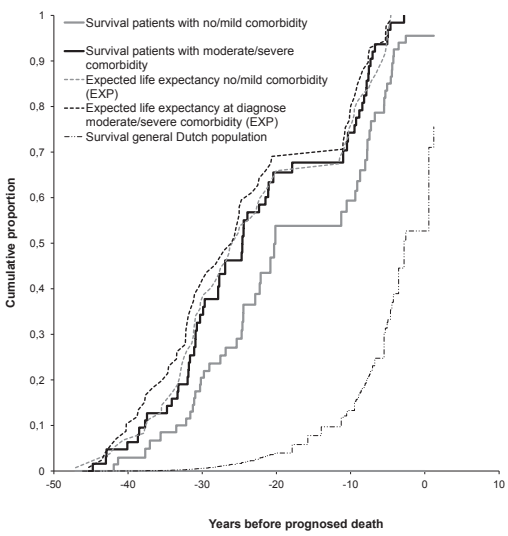


Figure 5a. Kaplan–Meier estimates of overall survival, subdivided over comorbidity in curatively treated pharyngeal cancer patients.

Figure 5b. Kaplan–Meier estimates of overall survival, adjusted to sex, age and birth cohort, subdivided over comorbidity in pharyngeal cancer patients. Rising comorbidity significantly decreases survival. Time base is based on negative life expectancy. The grey and black dashed line shows remaining life expectancy at diagnose of patients with no/mild comorbidity and moderate/severe comorbidity. In grey and black the survival of pharyngeal cancer patients with no/mild comorbidity and moderate/severe comorbidity is shown.

or radiation therapy.(Allal et al., 2000; Chin et al., 1995; J. P. Pignon et al., 2009; Schofield et al., 2003) Therefore, in most of these studies it was concluded that, aside from patients with severe comorbidity, major surgery or definitive radiation therapy can be performed safely in elderly patients. Our findings are in line with these studies, as we registered the same complication patterns in young and elderly pharyngeal cancer patients. The only difference between the two age groups was one elderly patient who died during radiation therapy. In the literature, a clear relationship was found between complications and comorbidity in head and neck cancer patients, especially in younger patients. (Borggreven et al., 2003; de Cassia Braga Ribeiro et al., 2003; Derks et al., 2005; Peters, van der Laan et al., 2011; Sanabria et al., 2008) In the univariate analysis of the present study, no significant association was found between age and complications or between age and comorbidity. In addition, in the multivariate analysis, high levels of co-morbid conditions were not significantly associated with treatment related complications. In this multivariate analysis of potential prognostic factors for complications, only tumor stage was found to be a significant factor.

Data in the literature on factors (ACE-27 score, T stage, age, anesthesia time) predicting treatment complications in head and neck cancer patients are somewhat controversial.

(Borggreven et al., 2003; Farwell et al., 2002; Ferrier et al., 2005; Kowalski et al., 1994; Suh et al., 2004) In studies reporting on radiation therapy in elderly head and neck cancer patients confirm that radiation therapy can safely be applied in the aged population, since same similar acute and late toxicities were found in young and elderly head and neck cancer patients treated by accelerated radiotherapy.(Allal et al., 2000; Chin et al., 1995; Schofield et al., 2003) In the present study, we found no significant association between the severity of co-morbid condition and survival. However, this relationship was found by the life expectancy analysis when adjusted for age and sex. Patients with no and mild co-morbidity had significantly longer life expectancies than patients with moderate and severe decompensation. In line with our life expectancy survival data, Datema et al.(Datema et al., 2010) found a clear relation between ACE-27 co-morbidity grade and overall survival in a head and neck cancer population. In this study age was found to be a significant negative predictor of overall survival in the multivariate analysis. In another study on hypopharyngeal cancer patients, (Homma et al., 2010) age, tumor stage, tumor subsite and co-morbidity were significant prognostic factors for overall survival. Co-morbidity was also found to be an independent prognostic factor in a large study (17,712 patients) of heterogeneous cancer patients by Picorillo et al.(Piccirillo, Tierney et al., 2004) It is remarkable that in the elderly age group, patient's choice, age itself and poor general health condition were the most frequently mentioned reasons for palliative treatment. In contrast, in the young age group, tumor extension was the most frequently mentioned reason for non-curative treatment. These data are completely in line with other studies. Derks et al.(Derks et al., 2005) found that advanced age, advanced tumor stage, marital status (widowed), co-morbidity, less pain and "considering length of life less important" were associated with the choice for non-standard treatment. Yellen et al.(Yellen, Cella, & Leslie, 1994) found that elderly patients tended to choose for a more conservative treatment, preferring shorter life expectancy over possible toxicity. Based on these data, we conclude that there is no evidence to treat elderly oropharyngeal and hypopharyngeal cancer patients different than younger ones. The lack of association between comorbidity and complications in both young and elderly patients is remarkable, suggesting difficulty in predicting treatment-related complications in both young and elderly pharyngeal cancer patients. Therefore very careful pre-treatment evaluation of both young and elderly should always be considered. As age does not predict complications in multivariate analysis further emphasize that elderly should be treated according to generally applied protocols and that age as such is not a reason to change treatment strategies that turned out to be most effective in randomized controlled trials.

Major surgery of malignant tumors in uncommon head and neck localizations in young and elderly patients

3.1 Comorbidity, complications and survival of sinonasal malignancies in young and elderly treated by surgery

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Introduction

Sinonasal malignancies are uncommon neoplasms. According to a recent Dutch study the present incidence is around 11 cases per 1.000.000 inhabitant per year in the Netherlands.(Kuijpens et al., 2012) These rare tumors include several histological subtypes, which makes it difficult to perform prospective trials or even to collect enough cases for larger retrospective studies. The most common histological subtypes are epithelial tumors with an incidence of 4.42 per million in Europe.(Van Dijk et al., 2012) The incidence of other subtypes, like mucosal melanoma, sarcoma and sinonasal tumors with neuroendocrine differentiation (STND) is even lower. The histological classification of these tumors is unfortunately not uniform in the literature which makes it even more difficult to compare different studies.

Sinonasal tumors are presenting typically in an advanced stage and have poor prognosis with an overall 5-year survival of 35-53%.(Blanch, Ruiz, Alos, Traserra-Coderch, & Bernal-Sprekelsen, 2004; Dulguerov, Jacobsen, Allal, Lehmann, & Calcaterra, 2001; Khademi, Moradi, Hoseini, & Mohammadianpanah, 2009) The cornerstone of the treatment of these malignancies is surgery and post-operative (chemo)radiotherapy. This combined modality treatment proved to be associated with the best survival. (Bhattacharyya, 2002; Blanco et al., 2004; Carrillo, Guemes, Ramirez-Ortega, & Onate-Ocana, 2005; Dulguerov et al., 2001; Guntinas-Lichius et al., 2007; Katz et al., 2002; Khademi et al., 2009) Although a great proportion of sinonasal cancer patients are elderly, the postoperative complication rate and predictors for complications and survival is poorly investigated in the aged population. Generally, there is an ongoing debate in the literature whether age is an independent predictor for post-treatment complication in head and neck cancer. Concerning paranasal cancer surgery, the only study focusing on this issue analyses purely craniofacial resection and includes different primary sites involving the skull base.(Ganly et al., 2011)

The aim of this study was to evaluate complications and survival of patients with nasal and paranasal malignancies, focusing on differences between elderly and younger patients undergoing surgery.

Subjects and Methods

Patients with cancer of the nasal cavity (C30.0 according to the ICD-O-3) and of the accessory sinuses (ICD-O-3: C31.0–C31.9)(Fritz, 2000) between 1995 and 2009, treated by surgery in the University Medical Center Groningen were extracted from the database of the Comprehensive Cancer Centre in the Netherlands. In this study, we retrospectively analyzed patients surgically treated with a curative intention for malignant

tumor of the nasal cavity or paranasal sinuses. Patients' and tumor characteristics, including age, sex, tumor site, stage (according to the AJCC 7th edition) and histological subtype were registered. Treatment parameters such as type and length of operation and eventual postoperative radiotherapy were extracted from medical records. Only therapeutic interventions were analyzed, diagnostic ones not. Patients were analyzed in two age groups; patients 70 years and older and patients under the 70.

Co-morbidity of all patients was registered using the Adult Comorbidity Evaluation 27 (ACE-27) index.(Piccirillo, Tierney et al., 2004) Complications were graded using the contracted form of the Clavien-Dindo classification of complications.(Clavien et al., 2009) It has been recently used to analyzed complications in head and neck cancer reconstructive surgery.(Perisanidis et al., 2012) This scoring system grades complications within one month after surgery (or longer in case of prolonged hospitalization) in five contracted form grades. Univariate significance was determined using the chi-squared test, survival analysis was performed using Kaplan Meier estimations and statistical differences in groups were determined performing logrank test. Only disease specific survival (DSS) data were included, as the analysis was performed in two different age groups, which hampers overall survival. DSS was defined as the time between surgery and death of patients due to locoregional recurrence or distant metastasis.
The review committee of the National Cancer Registration gave permission for this study as they considered privacy adequately covered. Historical cohort based studies on medical records do not need Institutional Review Board approval in the Netherlands since there is no health risk.

Results

Patients' characteristics

Characteristics of the surgical interventions are shown in Table1. We identified 103 patients who have undergone in total 107 interventions for sinonasal malignancy in our institution. There were 71 patients younger than 70 years and 32 patients 70 years old or older. The mean age of the younger group was 54 years and 76 years of the elderly. Most of the patients had advanced, stage 3 and 4 disease, slightly more advanced stages in the elderly, but the differences were not significant. Most of the primary tumors were found in the nasal cavity followed the maxillary sinus and ethmoid. We registered 73 surgical interventions in the younger and 34 in the elderly group. The most common surgical procedure was lateral rhinotomy followed by craniofacial resection and maxillectomy. The length of the surgery varied extremely, between 15 minutes and more than 12 hours. The mean length of the procedures differed significantly

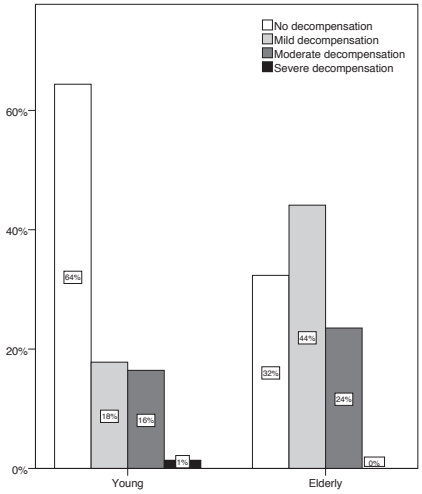

Figure 1. Distribution of co-morbidity according to the ACE-27 classification in surgically treated young and elderly patients with sinonasal malignancy. The differences in the two age groups are significantly different.

between the two groups at 252 minutes in the young population versus 154 minutes in the elderly. The most common histological subtypes were the epithelial tumors in both age groups counting for almost 60% of all patients, followed by sinonasal tumors with neuroendocrine differentiation in the younger population (27%) and melanoma in the elderly (27%). The majority, about 80% of the patients received postoperative radiotherapy in both patients' groups.

Co-morbidity

There were significant differences in co-morbidity data of the two examined populations. Elderly had a higher incidence and more severe co-morbidity than the young group. 64% of the young patients had no co-morbidity versus 32% of the elderly. Mild and moderate co-morbidity was registered in 18% and 16% of the young population and 44% and 24% of the elderly, respectively (Figure1).

Complications

Figure 2a shows the distribution of complications by grade in the young and elderly population. Most of the patients (roughly 65 %) had no complication in both groups. There were slightly more grade 2 complications in the younger group and more grade3 in de elderly, but these differences are not significant. No direct postoperative deaths were observed in either group. The types of complications differed slightly, but not statistically significant. Infection was more common in young (24% vs. 8% in elderly), while postoperative bleeding and fistula occurred more often in elderly (33% and 25% vs. 24% and 16% in young, respectively) (Figure 2b). We have also analyzed different factors affecting treatment related complications using multivariate analysis.

Table 1. Characteristics of included surgical interventions

	<70 y	≥70 y
Number of patients	71	32
Number of surgical interventions	73	34
Age (Years)		
Mean (range)	54 (16-69)	76 (70-88)
Sex (%)		
Male	39 (53)	23 (68)
Female	34 (47)	11 (32)
Stage (%)		
Stage I	10 (14)	3 (9)
Stage II	13 (18)	6 (18)
Stage III	5 (7)	8 (24)
Stage IV	28 (38)	15 (44)
Unknown	17 (23)	2 (6)
Site (%)		
Nasal cavity	30 (41)	23 (68)
Maxillary sinus	21 (29)	4 (12)
Etmoid sinus	10 (14)	6 (18)
Olfactory nerve	12 (16)	1 (3)
Surgery (%)		
Lateral rhinotomy	38 (52)	22 (65)
Craniofacial resection	16 (22)	1 (3)
Midfacial degolving	0 (0)	1 (3)
Maxillectomy	7 (10)	1 (3)
Endoscopic resection	2 (3)	2 (6)
Nose amputation	3 (4)	5 (15)
Neck dissection	4 (6)	0 (0)
Tumor resection	2 (3)	2 (6)
Caldwell-Luc	1 (1)	0 (0)
Length of surgery (minutes)		
Mean (range)	252 (50-766)	154 (15-405)
Histology (%)		
Epitelial tumor	43 (59)	20 (59)
Sarcoma	6 (8)	1(3)
Melanoma	4 (6)	9 (27)
Tumor with neuroendocrine diff.	20 (27)	4 (12)
Radiotherapy (%)		
No post-operative radiotherapy	10 (14)	7 (21)
Post-operative radiotherapy	63 (86)	27 (79)

Interestingly age, stage and co-morbidity are not found to be significant predictors of complications. However, the length of surgery appeared to be a strong factor, with an odds ratio of almost 3.5 (Table 2).

Follow-up

The median follow-up time in the whole group was 34 months, with a range of 1-195. The median follow-up time is 107 months in the survived patients with an interval between 13 and 195 months.

Survival

Using Kaplan Meier estimation, we analyzed the DSS of both age groups, which did not differ significantly from each other. The 5-years DSS lies around 60% in both groups (Figure 3). The disease specific survival per histological subtype has also been analyzed.

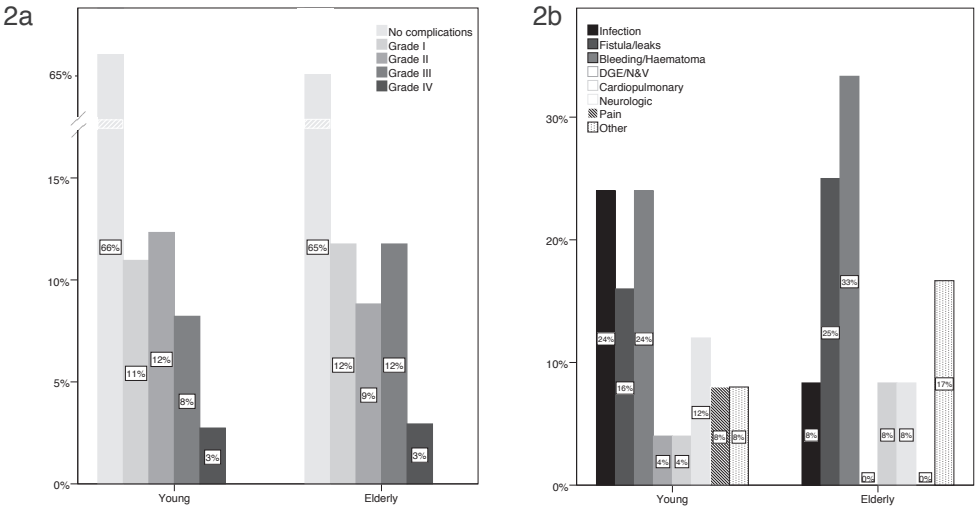

Figure 2. Distribution of complications according to the Clavien-Dindo classification in surgically treated young and elderly patients with sinonasal malignancy. Figure 2A shows the distribution of complications by severity score. The differences are not significant between young and elderly. Figure 2B demonstrates the distribution of complications by type of complication.

In the younger population best survival has been registered in the few cases of the sarcoma group, followed by STND and the epithelial tumors and far worst prognosis has been detected in the melanoma group (5-years DSS data are 83%, 68%, 57% and 0%, respectively). There was a significant in survival difference between these histologies (p=0.02) (Figure 4a). Contradictory to this, epithelial cancer had the best prognosis in the elderly population, followed by melanoma and STND (5-years DSS 67%, 63% and 50%, respectively). These differences were not significant (p=0.634) (Figure 4b).

Discussion

This is the first study analyzing co-morbidity, postoperative complications and disease specific survival in sinonasal malignancies focusing on differences between elderly (>=70 years) and young patients (<70 years). In our study, as expected, co-morbidity was more common in elderly patients. Despite of this, no significant difference was recorded in postoperative complications. This finding is very likely due to good patients selection in the elderly group, based on proper preoperative screening of patients. As only surgically treated patients were analyzed, there is surely a selection bias in the study population. We do not know how many patients and for what reason were not treated surgically. In multivariate analysis length of surgery was the only predictor for complication; age, stage and co-morbidity not. No significant difference was seen in disease specific survival of young and elderly patients. The survival of young patients differed significantly by histological subtype. However, in elderly patients no significant difference was seen in survival between histological subtypes.

Table 2. Multivariate analysis of factors affecting treatment-related complication in all patients.

Variable		Odds ratio (95% confidence interval)	P trend value
Age group (70 years and older)		1.453 (0.527-4.006)	0.470
Stage	Stage I	1 (ref)	0.467
	Stage II	1.413 (0.251-7.945)	
	Stage III	1.314 (0.205-8.430)	
	Stage IV	1.745 (0.372-8.182)	
Co-morbidity	No decompensation	1 (ref)	0.558
(ACE 27)	Mild decompensation	1.501 (0.482-4.675)	
	Moderate decompensation	1.603 (0.420- 6.116)	
Surgery > 160 min		3.499 (1.320-9.271)	**0.012**

Our finding, that co-morbidity is more frequent and more severe in elderly patients corresponds with other studies on head and neck cancer.(Paleri et al., 2010) The similar postoperative complication rate in young and elderly, observed in the present study is not really surprising. Previous papers on head and neck cancer patients had comparable findings,(Clayman et al., 1998; Kowalski et al., 1994; McGuirt et al., 1977; Peters et al., 2011) concluding that major head and neck surgery can also be safely performed in elderly after thorough preoperative evaluation. The present study analyzes only surgically treated patients, therefore the good patients selection for surgery is very likely the key to the not increased complication rate despite of higher occurrence of comorbid conditions. The postoperative complication rate of paranasal cancer sinus surgery has not been thoroughly investigated. The few studies focusing on postoperative complications almost all report exclusively on craniofacial resection. One exception is the study by Hanna et al. from 2009, finding an overall postoperative complication rate after endoscopic resection of sinonasal cancer as low as 11% regardless of whether a craniotomy was performed or not.(Hanna et al., 2009) This very favorable result is probably also due to the fact, that only surgical and not other complications were included in this study. The complication rate of ~35% in this study was in agreement with a large international multicentric study that found a 4.7% postoperative mortality and a 36.3% complication rate (including non surgical complications) after craniofacial resection of 1193 patients in 17 institutions.(Ganly et al., 2005) Co-morbidity was found to be the only significant predictor of mortality, while co-morbidity, prior radiotherapy and extent of intracranial tumor growth were independent predictors of postoperative complications. A more recent paper also analyzed the incidence of postoperative complications after craniofacial resection, varying between 29.7 and 54%. The postoperative complications of craniofacial resection are well described.(Ganly et al., 2011; Hentschel et al., 2004) In the most recent and largest series of Ganly et al.,(Ganly et al., 2011) the postoperative

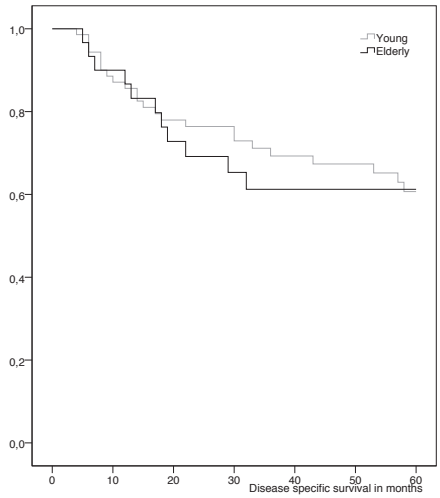

Figure 3. Disease specific survival (DSS) of surgically treated young and elderly patients with sinonasal malignancy. There is no significant difference in 5-years DSS between the young and elderly population.

complication rate in the elderly found to be as high as 42% and the mortality was 9%; both significantly higher than in the younger group. In this study age was found to be related to poorer survival. These data are difficult to compare with our results as our analysis includes different types of surgeries. However, our data contradicts the previous findings of these studies showing that age and co-morbidity are not independent predictors of complications. These conflicting data can be probably explained by careful patient selection in the operated population, especially in the elderly. To address this question all patients, thus the primarily irradiated or palliated patient population should be analyzed. On the other hand, we were the first to describe relationship between surgery time and chance of complication after sinonasal cancer surgery. The finding that longer surgery predicts postoperative complication is an important issue. It should stimulate surgeons to perform more simple and faster interventions, especially in older and frail patients.

Our disease free survival was around 65%, which is better than most recent published studies in the literature.(Blanch et al., 2004; Dulguerov et al., 2001; Katz et al., 2002; Khademi et al., 2009) Most of these studies also investigate predictors of survival. Data on age as an independent negative predictor of survival is controversial. Some authors found it significant factor,(Bhattacharyya, 2002) while others did not.(Khademi et al., 2009) Comparing survival of different age groups is difficult as the life expectancy of the healthy aged population is shorter. Therefore, we did not include overall survival analysis in our present study. We did not find differences in the disease specific survival of young and elderly patients in our series. Therefore we conclude that the (treatment of) sinonasal malignant tumor does not shorten life expectancy more in elderly patients. Thus, although elderly patients have a shorter a priori life expectancy, the similar tumor

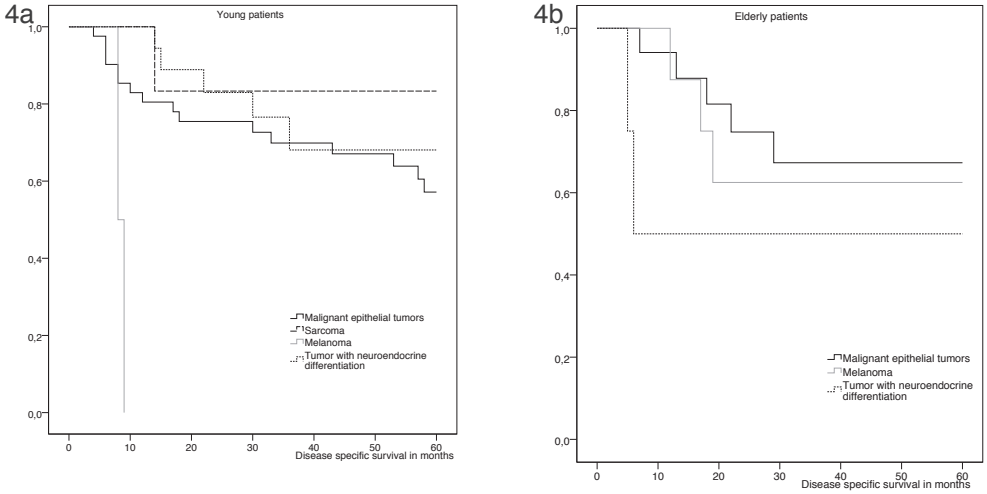

Figure 4. Disease specific survival (DSS) of surgically treated patients with sinonasal malignancy with different histological subtype. Figure 4A shows the DSS of young patients with different histology. The differences are statistically significant. Figure 4B shows the DSS of elderly patients with different histology. The differences are statistically not significant.

related survival should be a reason not to treat elderly patients differently. The analysis of survival in different histological subtypes brought interesting finding in our series; histology was not related to disease-specific survival in elderly patients. Most studies found the worst survival in patient with a malignant sinonasal melanoma,(Bentz, Bilsky, Shah, & Kraus, 2003; Ganly et al., 2011; Patel et al., 2003) our study only confirmed this in young patients. Some caution should be considered because only a small number of patients with melanoma were included. However the difference between young and elderly patient with sinonasal melanomas is striking.

In order to make better choices in the treatment of these patients a prospective study is needed. Our study cannot answer the question whether in which cases must surgical treatment be avoided as we did not include patients who were non-surgically treated. For the proper decision making of the multidisciplinary team, patients should be included with all treatment intentions and modalities. Not only treatment outcome but pre- and post-treatment quality of life analysis can also help in deciding whether it is worth these patients to operate. Based on this retrospective study, we can conclude that complications, survival and recurrence are not significantly different in young and elderly patients undergoing surgery for sinonasal malignancies. Therefore, based on this study, surgery can be also safely performed in elderly sinonasal cancer patients after careful preoperative evaluation and patient selection. As only surgically treated patients were included, the present study surely suffers from selection bias. In order to further investigate the risk of age in sinonasal cancer treatment a prospective study is needed.

Major surgery of malignant tumors in uncommon head and neck localizations in young and elderly patients

3.2 Predictors of postoperative complications and survival in patients with major salivary glands malignancies – a study highlighting the influence of age

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Introduction

Malignant tumors of the salivary glands are rare, in a recent study based on 76 population-based cancer registries in Europe an incidence of 13.07/1,000,000/year was found.(Van Dijk et al., 2012) It represents a group of tumors with different histological subtypes, primarily located at the parotid and submandibular gland.(Bjorndal et al., 2012) The cornerstone in the treatment of malignant major salivary tumors is surgery, and depending on tumor characteristics, followed by adjuvant radiotherapy.(Noh et al., 2010; Terhaard et al., 2005) Risk factors for malignant salivary gland tumors are not well established.(Guzzo et al., 2010) The highest incidence of malignant salivary gland tumors is in the 6th and 7th decade.(Pinkston & Cole, 1999) The rising percentage of elderly in the western population therefore suggests an increase of elderly patients with salivary gland malignancies in the future. Several studies show that comorbidity rates are more frequent in elderly patients.(Hocwald et al., 2001; Peters et al., 2011; Peters, van der Laan et al., 2011; Terhaard et al., 2008) However conflicting data exists regarding the treatment related complications in head and neck cancer in elderly patients.(Borggreven et al., 2003; Clayman et al., 1998; Kowalski et al., 1994; Peters et al., 2011; Peters, van der Laan et al., 2011; Suh et al., 2004) Little data is available on complications after treatment of malignant salivary gland tumor, and the predictive value of both age and comorbidity is unclear. Although no consensus is established regarding factors influencing complications and survival in elderly patients, elderly patients with head and neck cancer tend to be treated differently than their younger counterparts. (Derks et al., 2005) Several factors have shown to influence survival after treatment of malignant salivary gland tumors. Patient characteristics like male gender(Cheung, Franzmann, Sola, Pincus, & Koniaris, 2011) and age(Bell, Dierks, Homer, & Potter, 2005; Cheung et al., 2011) have been associated with a negative effect on survival. Terhaard et al.(Terhaard et al., 2008) found that comorbidity significantly influences overall survival, but not the disease free survival in malignant salivary gland tumor. Tumor characteristics like stage(Bell et al., 2005; Cheung et al., 2011; Hocwald et al., 2001; Noh et al., 2010; Oplatek, Ozer, Agrawal, Bapna, & Schuller, 2010; Terhaard et al., 2004), lymphovascular invasion(Kim et al., 2012; Noh et al., 2010; Oplatek et al., 2010) and perineural growth(Hocwald et al., 2001; Kim et al., 2012; Noh et al., 2010), had negative prognostic influence as well. The goal of this study is to find possible predictors of postoperative complications and survival for patients with malignant tumors of the major salivary glands with special interest in the influence of age.

Patients and methods

Patients

All patients with a malignant tumor of the major salivary gland (parotid and submandibular) treated surgically with curative intention between 1995-2010 in the University Medical Center Groningen (UMCG), Groningen, The Netherlands were retrospectively analyzed. All surgical procedures were separately included when patients required more than one operation. The primary database was obtained from the Comprehensive Cancer Centre of the Netherlands.

Clinical variables

Data were obtained using the paper and electronic medical chart database of the UMCG. Patient demographics included age, sex, tumor site and stage (using the seventh edition of the AJCC Cancer Staging Manual). Patients were divided into two age groups: patients 70 years and older and patients under 70. Tumor characteristics (perineural and lymphovascular invasion) were obtained from the histopathological examination report. Comorbidity of all patients was collected using the Adult Comorbidity Evaluation 27 (ACE-27) index. The ACE-27 index evaluates 27 cogent comorbid ailments subdivided over 12 different organ systems, separating them into no/mild/moderate and severe comorbidity.(Piccirillo, Tierney et al., 2004) Complications were evaluated using the Clavien-Dindo classification of complications (Table 1.).(Clavien et al., 2009; Dindo et al., 2004) This scoring system classifies complications, which occur within one month after surgery (or longer in case of prolonged hospitalization) in five (contracted form) or seven (in the full scale) grades. The contracted form was used. Postoperative facial nerve palsy was not recorded as a complication when it recovered over time without intervention or when facial nerve was sacrificed because of tumor invasion. Survival status and recurrence status were recorded in all patients.

Statistic analysis

The univariate statistical analysis, testing a possible association of comorbidity, complications in different age groups was conducted using the chi square test. Complications were divided into two categories: (1) Grade 0 and I and (2) Grade II-V complications. Multivariate logistic regression was performed to analyze the relation between age, comorbidity, tumor stage and complications. Survival analysis was performed using the Kaplan Meier method, and univariate differences in groups were analyzed with the logrank test. For multivariate survival analysis a Cox proportional hazards model was used. In the survival analysis, only the characteristics of the first surgical treatment per individual patient were included. Disease specific survival was

defined as the time between surgery and death of patients with locoregional recurrence or distant metastasis.

Results

Demographics

A total number of 111 surgical interventions for the treatment of malignant salivary gland tumors were performed in 108 patients between January 1995 and January 2010 (Table 2). There were 78 interventions performed in younger patients group and 33 in the elderly group. Most tumors were located in the parotid gland (76% in young patients, 88% in elderly patients). Only lymphovascular invasion was significantly lower in elderly patient compared to younger patients (p=0.028). No difference was seen in the use of post-operative radiotherapy. Furthermore no significant difference in the interval between surgery and radiotherapy was seen between both age groups.

Comorbidity

A significant difference was found in the occurrence of comorbidity in young and elderly patients (p=0.000) (Figure 1). Most young patients had no comorbidity at the time of treatment (78%), while the majority of elderly patients had mild comorbidity (42%). Higher comorbidity scores were more frequent in elderly patient.

Postoperative complications

Postoperative complications were significantly more frequent noted in elderly patients (p=0.026) (Figure 2), 30% in the elderly and in 17% of the younger. Not only the frequency but also the severity of the complications in elderly was higher. Nine percent of elderly patients had grade IV or V complications. Infection was the most frequent complication in young patients, while cardiopulmonary problems were the most common in elderly (Figure 3). Five patients suffered neurologic complications. Four patients had a persisting facial nerve pareses, and one patient had a cerebrovascular

Table 1. Classification of Surgical Complications according to Clavien and Dindo (contracted form)

Grade	Definition
Grade 0	No complication
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication
Grade V	Death of a patient

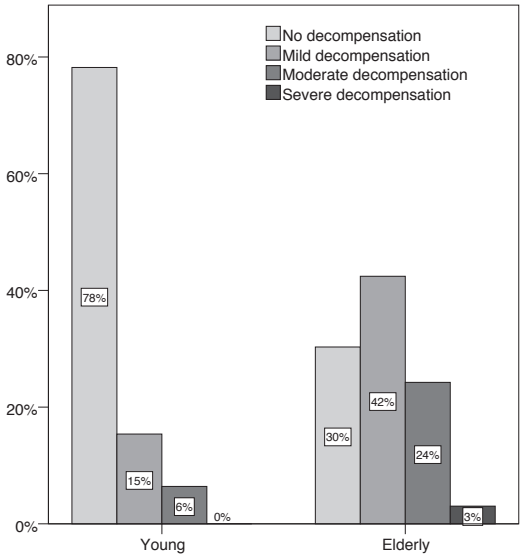

Figure 1. Distribution of comorbidity based on the Adult Comorbidity Evaluation 27 (ACE-27) test in young and elderly patients. The difference in distribution is significant (p=0.000).

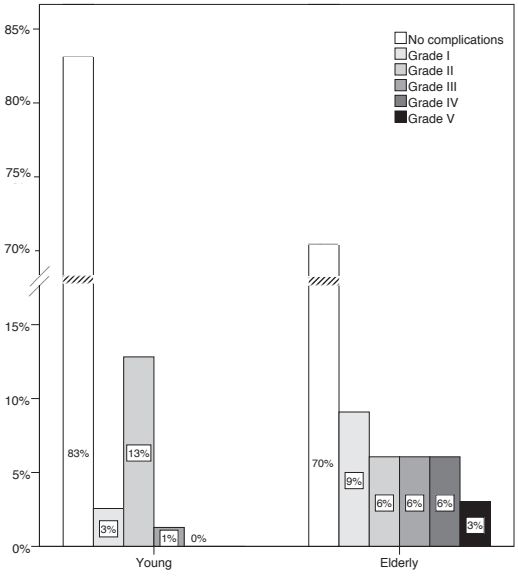

Figure 2. Distribution of complications based on the Clavien-Dindo classification in young and elderly patients. The difference in distribution is significant (p=0.026).

event. The remaining complications (defined as 'other') were wound dehiscence (2 patients), retention bladder (2) and psychological agitation (1). In an univariate analysis a significant association between comorbidity and complications was found in elderly patients (p=0.021). Although complications were significantly more common in elderly patients, age was no longer an independent factor for the occurrence of a complication multivariate analysis (Table 3). Only stage was a significant predictor of complications. The odds ratio for comorbidity (ACE 27) was 1.947 (CI: 0.425-8.926), however this was not statistically significant.

Survival

Table 4 shows univariate analysis outcome on possible predictors of overall and disease specific survival. Age, stage, ACE 27 grade, perineural growth and lymphovascular invasion were significant predictors of overall survival. However, in disease specific survival only stage, perineural growth and lymphovascular invasion were significant predictors. Age was no significant predictor of disease specific survival in univariate analysis (p=0.054). However the 5 years disease specific survival of patients 70 and over was 71% vs. 86% in younger patients. Multivariate analysis of prognostic factors of survival is shown in Table 5. In the multivariate analysis only stage was shown to be a significant predictor of disease specific survival (p=0.016). Age and stage were significant predictors of overall survival.

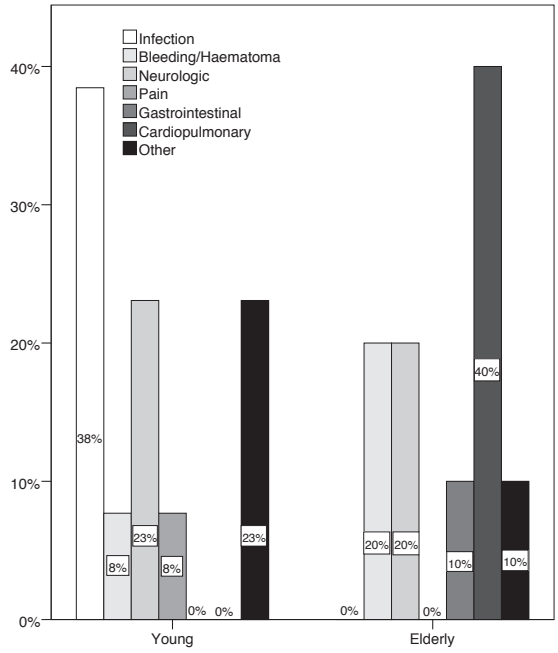

Figure 3. Type of complications in young and elderly patients, based on the Clavien-Dindo classification. The total number of complications in young patients was 13, and in elderly patients 10.

Discussion

This is the first study focusing on postoperative complications of young and elderly patients with malignant salivary gland tumor. This study shows a higher incidence of postoperative complications in elderly patients with salivary gland tumor, however age was not a predictor of complications in the multivariate analysis. Age was also not a significant predictor of disease specific survival. The analysis obviously suffers from the retrospective nature of this study. As only surgically treated patients are included in the present study resulting possibly in a selection bias.

The results of this study and previous studies(Terhaard et al., 2008) show a lower incidence of comorbidity in this patient group compared to other localizations within the head and neck.(Borggreven et al., 2003; Ferrier et al., 2005; Piccirillo, Spitznagel, Vermani, Costas, & Schnitzler, 2004; Sanabria et al., 2008) Very likely because alcohol abuse is a clear etiologic factor for other head and neck malignancies and is recorded in the ACE 27 classification. Like in other studies on different primary tumor sites(Paleri et al., 2010; Peters, van der Laan et al., 2011; Terhaard et al., 2008), the higher incidence of comorbidity in elderly patients is confirmed by us. In most studies complication rates after surgery for a head and neck malignancy are comparable in young and elderly patient. Therefore, these studies concluded that age alone is not a predictor of complications.(Beausang et al., 2003; Borggreven et al., 2003; Clayman et al., 1998; Peters et al., 2011; Peters, van der Laan et al., 2011) However, we found a higher

Table 2. Characteristics of included surgical interventions.

	No. of patients <70 y	No. of patients ≥70 y	P value
Total no.	78	33	
Age (Years)			
Mean (range)	49 (11-69)	78 (70-90)	
Sex (%)			0.718
Male	42 (54)	19 (58)	
Female	36 (46)	14 (42)	
*Stage (%) **			0.158
Stage I	18 (24)	4 (13)	
Stage II	20 (27)	5 (16)	
Stage III	8 (11)	5 (16)	
Stage IV	29 (39)	18 (56)	
Unknown	3	1	
Site (%)			0.146
Parotid gland	59 (76)	29 (88)	
Submandibular gland	19 (24)	4 (12)	
Salivary gland surgery (%) †			0.277
Superficial parotidectomy	9 (12)	1 (3)	
Subtotal parotidectomy	26 (33)	14 (42)	
Total parotidectomy	24 (31)	14 (42)	
Submandibular gland excision	15 (19)	4 (12)	
Neck dissection (%)			0.276
Elective neck dissection	34 (44)	12 (36)	
Therapeutic neck dissection	15 (19)	11 (33)	
No neck dissection	29 (37)	10 (30)	
Length of surgery (minutes)			0.714
Mean (range)	284 (60-860)	296 (80-667)	
Post operative radiotherapy (%)			0.619
No post operative radiotherapy	20 (26)	7 (21)	
Post operative radiotherapy	58 (74)	26 (79)	
Histology (%)			0.152
Adenoid cystic carcinoma	20 (26)	3 (9)	
Mucoepidermoid carcinoma	11 (14)	3 (9)	
Adenocarcinoma	17 (22)	13 (39)	
Acinic cell carcinoma	15 (19)	5 (15)	
Carcinoma ex-pleiomorphic adenoma	3 (4)	0	
Squamous cell carcinoma	1 (1)	2 (6)	
Epithelial-myoepiththelial carcinoma	1 (1)	1 (3)	
Salivary duct carcinoma	3 (4)	2 (6)	
Oncocytic carcinoma	3 (4)	0	
Large cell carcinoma	3 (4)	2 (6)	
Small cell carcinoma	1 (1)	0	
Angiosarcoma	0	1 (3)	
Spindle cell carcinoma	0	1 (3)	
Perineural invasion (%)			0.352
No perineural growth	44 (63)	17 (53)	
Perineural growth	26 (37)	15 (47)	
Unknown	8	1	
Lymphovascular invasion (%)			0.028
No lymphovascular invasion	53 (80)	19 (59)	
Lymphovascular invasion	13 (19)	13 (41)	
Unknown	12	1	

*Stage could not be scored in all patients, due to missing information
† Not all patients underwent surgery involving the primary tumor

incidence of complications in elderly in this study, as in some other studies.(Blackwell et al., 2002; Suh et al., 2004) In this study, the Clavien-Dindo classification system, validated and tested for interobserver variation, made it possible to uniformly classify the severity and nature of complications.(Clavien et al., 2009; Dindo et al., 2004) This

Table 3. Multivariate analysis of factors affecting treatment-related complication in all patients.

Variable		Odds ratio (95% confidence interval)	P trend value
Age group at diagnose		0.960 (0.278-3.322)	0.949
Stage	Stage I	No complications	0.006
	Stage II	1 (ref))	
	Stage III	2.564 (0.301-21.801)	
	Stage IV	5.725 (1.079-30.366)	
Comorbidity (ACE 27)*		1.947 (0.425-8.926)	0.391
Length of surgery †		0.933 (0.258-3.379)	0.916

*No/mild comorbidity vs. moderate/severe comorbidity
† Divided over two groups: < than 240 minutes vs. ≥ than 240 minutes (median time of surgery)
Abbreviations; ACE 27: Adult Comorbidity Index 27

system has already been used for evaluation of postoperative complications of head and neck cancer.(Perisanidis et al., 2012) Studies on postoperative complications after parotid surgery are mostly performed on patients with benign lesions.(Ciuman, Oels, Jaussi, & Dost, 2012; Maddox, Paydarfar, & Davies, 2012) They show complication rate between 10% and 24% (excluding facial nerve paralysis), however these results are difficult to compare to the results in this study due to the different nature of the pathology. Only surgically treated patients were included in this study, which can hamper generalizability of our data. Treatment outcome of patients treated with radiotherapy alone or treated with palliative intention were not analyzed. Therefore it is unclear how many patients were treated differently and for what reasons, especially in elderly patients and patients with more severe comorbidity. To answer this question is difficult, based on a retrospective analysis. A thorough analysis would require a prospective study, however Terhaard et al. have tried to answer this question in their retrospective study, where patients with higher comorbidity were reported to receive non-standard treatment more often.(Terhaard et al., 2008) No differences between young and elderly were seen in our study with respect to the proportion of patients receiving radiotherapy after surgery , indicating that elderly patients equally received optimal treatment. Furthermore, no prolonged period of recovery was necessary before the start of radiotherapy. However included patients were deemed to have acceptable risks to undergo surgery, and therefore no universal conclusion can be made for patients with salivary gland malignancies.

Several studies describe a relation between (especially severe) comorbidity and complications.(Beausang et al., 2003; Ferrier et al., 2005; Peters et al., 2011; Peters, van der Laan et al., 2011; Suh et al., 2004) This relation is debated in elderly patients with head and neck cancer.(Beausang et al., 2003; Borggreven et al., 2003; Peters et

Table 4. Univariate analysis of factors influencing survival of patients with a malignancy of a major salivary gland.

Factors		Disease specific survival 5 yr survival %	*P*-value	Overall survival 5 yr survival %	*P*-value
Age (yr)					
	<70	86	0.054	78	**0.000**
	≥70	71		42	
Gender					
	Male	79	0.506	66	0.257
	Female	85		74	
Stage					
	Stage 1	100	**0.000**	100	**0.000**
	Stage 2	100		88	
	Stage 3	92		68	
	Stage 4	56		38	
Comorbidity (ACE 27)*					
	Grade 0/1	83	0.420	72	**0.004**
	Grade 2/3	69		36	
Perineural growth					
	No perineural growth	87	**0.032**	77	**0.006**
	Perineural growth	70		50	
Lymphovascular invasion					
	No Lymphovascular invasion	88	**0.006**	79	**0.000**
	Lymphovascular invasion	66		32	

Abbreviations; ACE 27: Adult Comorbidity Index 27

al., 2011; Peters, van der Laan et al., 2011) Although the present study found higher comorbidity and complication rate in elderly, multivariate analysis did not confirm the predictive role of comorbidity in the development of complications. The difference found with univariate analysis in complications can be explained by the higher frequency of advanced staged tumor in the elderly patients (37% stage IV in young and 55% in elderly patients). Other studies evaluating surgically treated elderly patients with other head and neck malignancies have also not shown higher complication rate in elderly patients.(Clayman et al., 1998; Kowalski et al., 1994; Peters et al., 2011; Peters, van der Laan et al., 2011) To our knowledge, this is the first study evaluating complications in this specific group of patients.

In this study only stage was found to be good predictor of complications; no other strong predictor of complications was found in elderly patients with salivary gland malignancies. Although a relation of stage with the length of operation seems apparent, no difference was seen between young and elderly patients. Furthermore, in multivariate testing length of surgery did not independently predict complications. A possible explanation of the correlation between stage and post-operative complications is the fact that advanced

Table 5. Multivariate analysis of prognostic factors for disease specific survival and overall survival in malignant salivary gland tumors.

	Disease specific survival		Overall survival	
Factors	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**
Age	0.147	2.401 (0.736-7.833)	**0.009**	2.992 (1.307-6.847)
Gender	0.454	0.655 (0.216-1.981)	0.385	0.706 (0.321-1.550)
Stage	**0.016**	8.240 (1.486-45.703)	**0.000**	2.550 (1.525-4.264)
Comorbidity (ACE 27)*	0.495	0.594 (0.133-2.651)	0.987	0.992 (0.387-2.546)
Perineural growth	0.527	0.714 (0.251-2.032)	0.551	0.792 (0.367-1.707)
Lymphovascular invasion	0.355	1.700 (0.552-5.232)	0.096	1.974 (0.887-4.393)

*No/mild comorbidity vs. moderate/severe comorbidity
Abbreviations; CI: confidence interval; ACE 27: Adult Comorbidity Index 27

disease necessitates more extensive surgery. Although some previous studies found a relation between complications and stage in other head and neck malignancies,(de Cassia Braga Ribeiro et al., 2003; Peters et al., 2011; Peters, van der Laan et al., 2011) addition research is needed to further explore the influence of stage on complications.
Age was not a significant predictor for disease specific survival, contradicting the results of Terhaard et al.(Terhaard et al., 2008) and Bell et al.(Bell et al., 2005). This difference probably comes from the lower number of patients in our study and possibly also from selection bias (including only surgically treated patients), and although not statistically significant, a trend towards worse disease specific survival in elderly was visible. The only factor that was a significant predictor of survival was stage, which corresponds with other studies.(Al-Mamgani, van Rooij, Sewnaik, Tans, & Hardillo, 2012; Bell et al., 2005; Hocwald et al., 2001; Kim et al., 2012; Noh et al., 2010; Oplatek et al., 2010; Terhaard et al., 2004; Terhaard et al., 2008) Other tumor related factors, like perineural growth and lymphovascular invasion predict survival only in the univariate analysis and are therefore not independent prognostic factors, as in some earlier studies.(Kim et al., 2012; Noh et al., 2010; Oplatek et al., 2010) In the larger study by Terhaard et al.(Terhaard et al., 2008) the possible role of comorbidity in survival was analyzed. This study also used the ACE-27 comorbidity index as a basis for analysis, therefore the results are comparable with this study. Terhaard et al. concluded that only overall survival and not disease free survival was predicted by comorbidity. Similarly to these results, we did not identify comorbidity as an independent factor of disease specific survival. According to our results life expectancy of patients with malignant salivary gland tumor is not influenced by age, nor by comorbidity. Again, only stage of the tumor negatively influenced the disease specific survival. The result that overall survival is influenced by age, is not surprising. We therefore conclude, that malignant salivary gland tumor reduces the tumor related life expectancy equally in both age groups, and therefore should not be a reason for non-standard treatment. Once more, these data

should be confirmed by a prospective study, including patients receiving standard and non-standard treatment.

Conclusions

In conclusion, the results of this retrospective study reviewing surgically treated patients with major salivary gland malignancies show a higher incidence of complications in elderly patients. However the complication rate was not associated with age or comorbidity in multivariate analysis, only tumor stage was an independent predictor of complications. The higher occurrence of complications in elderly should be taking into account when treating and caring for elderly patients. Disease specific survival was not significantly different in elderly patient, and therefore age is not a reason to treat elderly differently. However the higher occurrence of comorbidity in elderly implies the need of extra preoperative assessment and postoperative care.

The clinical outcomes and influence of age after free-flap surgery

4.1 Free flap reconstruction for head & neck cancer is not necessarily riskier in elderly patients

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Submitted

Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world, with approximately 650,000 new cases and 350,000 cancer deaths each year.(Parkin, Bray, Ferlay, & Pisani, 2005) Surgery is one of the cornerstones in the treatment of HNC, irrespective of age.(Bernardi et al., 2005) Surgical ablation often results in complex defects that disturb aesthetic contours and impair oral, pharyngeal and laryngeal functions. Microvascular free tissue transfer revolutionized head and neck reconstruction, and is frequently used to try and achieve the most optimal functional and aesthetic result. Due to advances in surgical technique and instrumentation, microvascular surgery has reached a success rate of over 95% in large centers.(Chen et al., 2007; Gusenoff et al., 2006; Novakovic, Patel, Goldstein, & Gullane, 2009; Wolff, Holzle, Wysluch, Mucke, & Kesting, 2008; Wong & Wei, 2010) Although the peak incidence of HNC is between the fifth and sixth decade, an estimated 25% of HNC is found in patients above 70 years. (Ferrari et al., 2013; Muir, Fraumeni, & Doll, 1994; Syrigos et al., 2009) The suitability of elderly patients as candidates for major reconstructive surgery remains controversial, and there are limited data available on this topic. Some authors state that elderly patients should be treated similarly to the younger ones(Derks et al., 2004; Derks, De Leeuw, Winnubst, & Hordijk, 2004; Derks et al., 2005; Lalami et al., 2009; Sesterhenn et al., 2005), though several studies have shown that elderly patients are less likely to receive standard treatment.(Bernardi et al., 2005; Derks et al., 2005; Hirano & Mori, 1998; Sarini et al., 2001) Curative treatment with radical surgery is often withheld based on age, while opting for more conservative therapy.(Boruk et al., 2005; Derks et al., 2005) Not only the incidence, but also the clinical consequences of post-operative complications are important factors to assess suitability of elderly patients for major surgery. The objective of this study is to retrospectively analyze treatment outcome after primary free flap reconstruction for head and neck cancer using the Clavien-Dindo classification, and compare elderly patients to younger counterparts.(Dindo et al., 2004)

Patients and methods

Patients

A retrospective review was conducted of all surgically treated patients diagnosed with HNC between January 1995 and January 2010 at the University Medical Center Groningen (UMCG), The Netherlands. This primary database was acquired from the Comprehensive Cancer Center of The Netherlands. All patients who underwent primary free flap reconstruction directly following or shortly after surgery for primary HNC were included in this study. Patients undergoing free flap reconstruction for treatment of a complication (e.g. wound break down) after primary surgery were not included.

Clinical variables

Electronic and paper medical charts were used to obtain patient, tumor, and treatment information including age, sex, tumor site, stage, surgical treatment, and type of free flap reconstruction. The Adult Comorbidity Evaluation 27 (ACE-27) index was used to score comorbidity using four categories: no/mild/moderate/severe comorbidity. (Piccirillo, Tierney et al., 2004) The Clavien Dindo classification was used to evaluate complications according to five different grades (contracted form).(Clavien et al., 2009; Dindo et al., 2004) We categorized complications as related to acceptor site, donor site, and medical complications. Complications related to tumor surgery were not analyzed. Post-operative complications that occurred during the first month or during hospital stays exceeding one month were scored. Analysis was also performed by comparing young (<70 years) and elderly (≥70 years) patients.

Statistical analysis

Univariate statistical analysis using a chi square test was performed to assess differences between age groups and the effect of comorbidity on complications. For multivariate testing, a logistic regression analysis was conducted, and the dependent variable was divided into grades 0-II (no complications to minimal complications) and grade III-V (minimally requiring surgical, endoscopic or radiological intervention). Survival was analyzed using a multivariate Cox regression analysis. Disease specific survival was defined as the percentage of patients who survived HNC for a defined period of time, calculated from start of treatment until time of death. Patients who died from causes other than HNC were censored in the calculation. Overall survival was defined as the lifetime duration calculated from start of treatment for patients diagnosed with HNC who were still alive at time of data analysis. Overall survival rate is the percentage of HNC patients still alive for a certain period of time after start of treatment.

Results

Demographics

Two hundred and two patients were included in this study. Demographic information is shown in Table 1. Most patients had a stage IV tumor (61%) originating from the oral cavity (67%). The most common type of reconstruction was a radial forearm flap, in 56% of the patients. One hundred and sixty nine patients <70 years, and 33 patients ≥70 years were included. There was no significant difference in baseline characteristics between young and elderly patients, including comorbidity.

Table 1. Patient characteristics.

	All
N	202
Age (Years)	
<70 y	169 (84)
≥70 y	33 (16)
Sex n(%)	
Male	129 (64)
Female	73 (36)
Stage n(%)	
Stage I	7 (3)
Stage II	30 (15)
Stage III	37 (18)
Stage IV	124 (61)
Tumor site n(%)	
Lip	1 (1)
Oral cavity	135 (67)
Oropharynx	42 (21)
Hypopharynx	15 (7)
Larynx	2 (1)
Nasal cavity and paranasal sinuses	2 (1)
Major salivary glands	4 (2)
Skin/bone/connective tissue	1 (1)
Surgical treatment n(%)	
Glossectomy	21 (10)
Mandibulectomy	136 (67)
Total laryngectomy	15 (7)
Parotidectomy	2 (1)
Maxillectomy	4 (2)
Tumor resection	23 (11)
Petrosectomy	1 (1)
Type of free flap n(%)	
Anterolateral thigh flap	9 (4)
Radial forearm flap	114 (56)
Rectus abdominis flap	2 (1)
Fibula flap	66 (33)
Ulnar forearm flap	2 (1)
Iliac crest flap	4 (2)
Jejunum flap	5 (2)
Gracilis flap	1 (1)
Pre-operative radiotherapy n(%)	
No	192 (95)
Yes	10 (5)
Pre-operative comorbidity n(%)	
None	45 (22)
Mild	72 (36)
Moderate	69 (34)
Severe	16 (8)

Complications

There were 121 patients (60%) with a total of 139 complications (Table 2). There were 63 minor complications and 76 major complications. The majority of complications were medical (40%), followed by recipient site (26%) and donor site (4%) complications. The majority of medical complications were minor (57%), mostly Clavien Dindo grade II. However, there were a relatively large number (27) of life-threatening or fatal complications (grade IV and V). Recipient site complications were mostly grade III (thus requiring re-intervention). Only one grade V complication was recorded in relation to

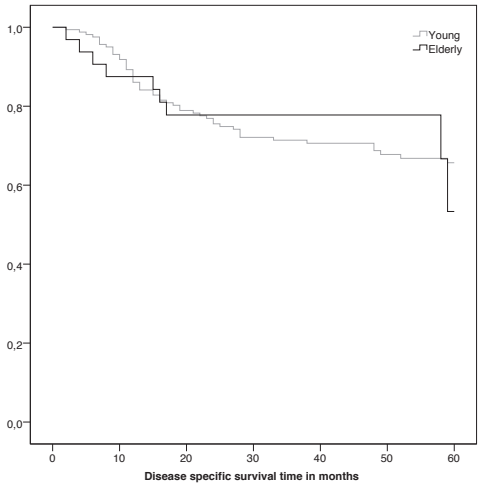

Figure 1a. Disease specific survival in young and elderly patients after free flap surgery for reconstruction after a surgical intervention for HNC

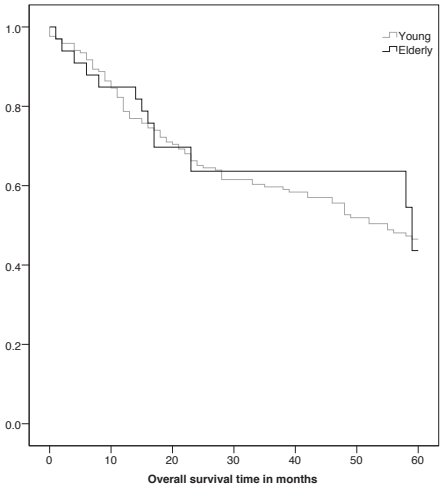

Figure 1b. Overall survival in young and elderly patients after free flap surgery for reconstruction after a surgical intervention for HNC

the recipient site. Only eight donor site complications were registered (seven in young patients and one in an elderly patient). This number is too low to conduct further analysis.

One-hundred and sixteen complications developed in the young group and 23 in the elderly group, taking into account the difference in group sizes (n=169 vs. n=33). There were 27 grade IV or V grade (life-threatening /resulting in death) complications in the young group, while only one (3%) elderly patient had a grade IV (life-threatening) complication. Young patients had significantly more medical complications compared to their elderly counterparts (p=0.024).

In multivariate analysis of recipient complications (Table 3) only disease stage II had significantly less complications compared to stage IV (p=0.047). Other possible predicting factors such as age, length of surgery, comorbidity, and type of flap reconstruction did not significantly predict major complications. Major medical complications were

Table 2. Total number of complications (n=139) according to the Clavien Dindo classification, categorized by recipient site, donor site, and medical complications.

	Recipient site n(%)	Donor site n(%)	Medical n(%)
Grade I	3 (2)	1 (1)	12 (9)
Grade II	10 (7)	4 (3)	33 (24)
Grade III	38 (27)	3 (2)	7 (5)
Grade IV	0	0	23 (17)
Grade V	1 (1)	0	4 (3)
Total	52 (37)	8 (6)	79 (57)

Table 3. Multivariate logistic regression analysis of major complications associated with recipient site and medical complications

		Recipient site complications		Medical complications	
Variable		Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age group	Elderly	0.56 (0.25-2.14)	0.559	0.89 (0.29-2.79)	0.845
Stage	Stage I	1.23 (0.22-6.99)	0.814	No cases	
	Stage II	**0.12 (0.02-0.97)**	**0.047**	0.50 (0.13-2.00)	0.329
	Stage III	0.49 (0.15-1.57)	0.228	2.31 (0.84-6.35)	0.105
	Stage IV	1 (ref)		1 (ref)	
ACE 27	≥ grade 2	1.161 (0.76-1.77)	0.489	**2.89 (1.71-4.84)**	**0.000**
Length of surgery	≥ 738 minutes (median)	0.912 (0.41-2.04)	0.822	1.03 (0.44-2.43)	0.942
Type of flap	Radial forearm flap	1 (ref)		1 (ref)	
	Fibula flap	1.65 (0.72-3.80)	0.237	1.25 (0.48-2.28)	0.646
	Other free flap	0.61 (0.13-2.98)	0.542	1.44 (0.40-1.19)	0.650

independently significantly predicted by comorbidity (ACE-27 grade 2 or higher), but not by other factors. As with recipient site complications, age, length of surgery, and type of flap did not significantly predict major complications. Furthermore, disease stage was not a significant predictor of medical complications.

Survival

In both disease specific survival and overall survival only stage IV tumors predicted a worse outcome, although there was only a significant difference with stage III (Table 4). All other factors- including age and comorbidity- did not have a significant impact on survival outcome. Figure 1a shows the disease specific survival in both age groups; the 5-year disease specific survival is 66% in young patients, and 53% in elderly patients. Figure 1b shows the overall survival: no significant difference was seen between the age groups (p=0.770).

Discussion

In this study, an analysis was done of possible predictors of complications and survival in HNC patients following free flap reconstruction after major surgery. In our study population, disease stage was the only significant independent predictor of recipient site complications, and comorbidity the significant predictor of medical complications. Furthermore, disease stage was the only significant predictor of survival. Other factors- including age- did not predict disease specific nor overall survival.

The overall complication rate in our study population was 60%. A recent prospective study(McMahon et al., 2013) analyzed complications after major head and neck surgery with free flap repair and found a complication rate of 64%, with a major complication rate of 32%. These results are very similar to ours. Perisanidis et al.(Perisanidis et al.,

Table 4. Multivariate Cox regression of disease specific and overall survival of patients after free flap surgery

		Disease specific survival		**Overall survival**	
Variable		Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age group	Elderly	0.93 (0.43-1.99)	0.848	0.95 (0.52-1.73)	0.865
Stage	Stage I	No cases		0.36 (0.09-1.46)	0.152
	Stage II	0.39 (0.15-1.01)	0.053	0.62 (0.33-1.17)	0.137
	Stage III	**0.35 (0.15-0.86)**	**0.022**	**0.53 (0.28-0.99)**	**0.045**
	Stage IV	1 (ref)		1 (ref)	
ACE 27	≥ grade 2	0.84 (0.48-1.46)	0.526	1.11 (0.74-1.68)	0.621
Length of surgery	≥ 738 minutes (median)	0.97 (056-1.68)	0.924	1.232 (0.80-1.89)	0.339
Type of flap	Radial forearm flap	1 (ref)		1 (ref)	
	Fibula flap	0.82 (0.31-2.16)	0.690	0.591 (0.31-1.13)	0.112
	Other free flap	0.91 (0.34-2.45)	0.858	0.729 (0.37-1.43)	0.359

2012) retrospectively analyzed complications after head and neck reconstruction with a jejunal free flap, and found a complication rate of 85% and a major complication rate of 65%. This could be explained because the jejunal free flap is relatively unreliable type of flap. Overall however, there is considerable heterogeneity and inconsistency in literature, due to subjective interpretation and non-standard reporting of complications. (Perisanidis et al., 2012) This makes comparison with other studies very difficult. In order to avoid this problem, recent studies recommend the Clavien Dindo classification for evaluation of postoperative complications after head and neck free flap surgery. (Perisanidis et al., 2012) This is an objective, reliable, and reproducible classification system that ranks complications by severity based on the intervention used to treat the complications.(Clavien et al., 2009; Dindo et al., 2004)

Our data show that elderly patients who underwent free flap reconstruction did not have a significantly higher incidence or severity of complications than younger patients. These results are in concert with various previous studies that evaluated the outcome of major surgery in elderly patients.(Beausang et al., 2003; Ferrari et al., 2013; Milet et al., 2010; Shaari & Urken, 1999; Vaz, Cote, Harris, & Seikaly, 2013; Zabrodsky et al., 2004) Patient selection should not occur based solely on chronological age, but requires risk assessment based on comorbidity as well.(Beausang et al., 2003; Boruk et al., 2005; Serletti, Higgins, Moran, & Orlando, 2000) Preexisting medical problems have been shown to have a strong correlation with poor post-operative outcome.(Beausang et al., 2003; Boruk et al., 2005; Ozkan et al., 2005) In elderly patients specifically, determining the patient's biological age is essential to assess whether a patient is fit enough for surgery. In addition to comorbidity, disability and especially frailty can be important factors that affect patients' biological age.(Drubbel et al., 2013; Fried, Ferrucci, Darer, Williamson, & Anderson, 2004)

In our study, disease stage was the only significant predictor of poorer disease specific and overall survival. Both age and comorbidity did not have a significant impact on survival outcome. These results differ from a previous study that found a significantly worse 5-year survival in oral cavity cancer patients ≥66 years, compared to younger age groups.(Funk et al., 2002) In their study, the five year survival per age group was as follows: 57.0% in ≤35 years, 52.9% in 36-65 years, and 49.1% in ≥66 years. However, our study indicates that elderly patients did not have a poorer disease specific or overall survival after free flap surgery. This difference in results could be explained by the fact that we only analyzed surgically treated patients. To our knowledge, we are the first to analyze survival after free flap reconstruction in elderly HNC patients.

The foremost limitation of this study is the selection bias, preventing generalization of the results. Elderly patients with head and neck malignancies generally have multiple and more severe comorbidity.(Peters, van der Laan et al., 2011; Piccirillo & Vlahiotis, 2006) The general health of elderly patients in this study population was not significantly different from the younger patients. This indicates that relatively healthy elderly patients were included in this study. Previous studies have shown that this selection is necessary to maximize the outcome of major surgery and microvascular reconstruction. (Borggreven et al., 2003; Borggreven et al., 2005; Sanabria et al., 2007; Sanabria et al., 2008; Suh et al., 2004; Vandersteen et al., 2012) All patients at our hospital go through a rigorous diagnostic protocol (including assessment of the vascular state) to determine eligibility for free flap surgery, as well as extensive evaluation by clinicians. A study by Derks et al.(Derks et al., 2005) concluded that age still influenced treatment choice, even after correction for comorbidity. Treatment selection is therefore most likely based on patient preference, as well as clinicians' possible prejudice of elderly patients' tolerance. (Derks et al., 2005; Sanabria et al., 2007) The aforementioned selection procedures are necessary, though selection based on personal opinions and assumptions cannot be ruled out. In order to avoid selection bias and to further investigate the relation between comorbidity and complication in elderly patients, a prospective study is needed.

Stringent selection was performed, which is reflected by the high percentage of absent or mild preoperative comorbidity. Severe comorbidity was seen in 9% of young patients and 3% of elderly patients. It is remarkable that severe comorbidity was accepted more often in younger patients planned for free flap reconstruction. This may explain the surprising outcome that disease specific survival was not statistically significantly different.

Conclusions

If careful patient selection is done, free flap reconstruction can be performed safely in both young and elderly HNC patients. Patients' biological age, and not the chronological age, should be individually determined to assess feasibility of major surgery. Optimal patient selection requires a thorough pre-operative assessment, including analysis of comorbidity in all patients. For a fair judgment of differences in the outcome of free flap surgery in young and elderly HNC patients, a prospective study would be needed.

Differences in type of comorbidity and complications in young and elderly

5.1 Relation between age, comorbidity, and complications in patients undergoing major surgery for head and neck cancer

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Introduction

Head and neck cancer is the sixth most common site for malignant tumors in the world.(Parkin et al., 2005) Surgery plays an important role in the treatment of these malignancies. Beside poor prognosis, high chance of postoperative complication makes the choice of an extensive surgery difficult. Efforts have been made to evaluate specific complications after head and neck surgery and the role of predictive factors. For instance, cardiovascular complications are found to be predicted by pre-existing (pulmonary) comorbidity and age(Buitelaar, Balm, Antonini, van Tinteren, & Huitink, 2006), and similar results are found for respiratory complications.(Buitelaar et al., 2006) However, in another study comorbidity or age did not predict wound infection after major head and neck surgery.(Milet et al., 2010) These studies focus on a specific complication after surgery only, and do not evaluate all complications.

A rise of 43% of the elderly population (aged 65 years and older) is projected for 2020 in the United States; the expected number of procedures performed for head and neck rising accordingly.(Bhattacharyya, 2011) It has been shown that comorbidity and complications are related (Ferrier et al., 2005); and it is well-known that comorbidity is more frequent in elderly patients. Increasing number of studies aim to answer the question whether elderly should receive these treatments or whether a selection is possible to determine a prosperous outcome.(Borggreven et al., 2003; Boruk et al., 2005; Derks et al., 2005; Peters et al., 2011; Peters, van der Laan et al., 2011; Sanabria et al., 2008; Sesterhenn et al., 2005; Zabrodsky et al., 2004) However, the role of comorbidity in the prediction of complications in elderly head and neck cancer patients is not that obvious. Some authors suggest a major role of especially severe comorbidities in the occurrence of complications in elderly patients.(Borggreven et al., 2003; Boruk et al., 2005; Derks et al., 2005; Sanabria et al., 2008; Sesterhenn et al., 2005; Zabrodsky et al., 2004) The aim of this study is to evaluate not only the occurrence and predictors of complications after major head and neck surgery, but also to discover relation between the type of complications and different comorbid conditions, with a special focus on elderly patients.

Patients and methods

Patients

Patients with head and neck cancer (lip and oral cavity, oropharynx, hypopharynx, larynx, nasal cavity, major salivary gland, malignancies of the ear and connective tissue malignancies) surgically treated between 1995-2010 in the University Medical Centre Groningen (UMCG), Groningen, The Netherlands were retrospectively analyzed. These

patients were acquired using the register of the Comprehensive Cancer Centre The Netherlands. Only patients were included in the present study with an operation time of more than 120 minutes, which indicates a major intervention in head and neck malignancies.(Buitelaar et al., 2006) When patients had more than one intervention for recurrent or second primary tumor, all interventions were included separately.

Clinical variables

Patients' data was gathered using the electronic medical chart. When digital data was incomplete, the paper based chart was reviewed. The collected data included age, sex, tumor site and TNM classification (AJCC Cancer Staging Manual 7th edition). Comorbidity was scored using the Adult Comorbidity Evaluation 27 (ACE-27) index. The ACE-27 classifies comorbidity into 4 different grades (no (0), mild (1), moderate (2) and severe (3) comorbidity). The ACE-27 severity of comorbidity is based on 26 cogent comorbid ailments divided over 12 different organ systems.(Piccirillo, Tierney et al., 2004) The specific organ system in which the comorbidity occurred was documented, and, if more than one, all affected organ systems were registered.

Complications were scored using the Clavien-Dindo classification.(Clavien et al., 2009; Dindo et al., 2004) This classification is primarily based on the need for intervention of the complication, and divides the complications into 5 grades. The grades range from grade I (minor deviation from normal postoperative course) to grade V (death of a patient). Only the most severe complication is graded. The time frame in which complications are scored is within one month, or until the date of discharge if hospitalization exceeded one month. We counted only complications grade II or higher as complication because grade I represent only minor deviations from the normal post-operative course when no intervention needed. Another component of the Clavien-Dindo classification (CDC) is the type of complication, where 11 possible types can be scored. In patients with more than one type of complication, all types of complication were scored. Eventually we have put all complications into three categories: (1) cardiopulmonary/neurologic complication (requiring internal medicine approach), (2) fistula, leaks, bleeding and hematoma (requiring surgical approach) and (3) infection (mostly requiring antibiotics). Infection can be both based on medical and surgical complication, but studied together for more reasons: (1) the primary source of an infection is not always clear (2) the treatment of infection is comparable in both cases and (3) the CDC analyzes complications according to their treatment.

Patients were analyzed in five different age groups (under 50 years, 50-60, 60-70, 70-

80 and 80 and over). Surgery violating the aero-digestive tract included glossectomy, mandibulectomy, total laryngectomy and tumor resection in aero-digestive tract (not classified in earlier categories).The intervention time was divided into four categories, based on the four quartiles in the data.

Statistical analysis

Univariate analysis of different variables was conducted using logistic regression analysis. For multivariate analysis all independent variables that significantly affected the severity of complications in univariate analysis were selected, completed with age group. As in univariate analysis only complications graded CDC II and higher were considered events. Comorbidity was analyzed dividing them over the different organ systems in the ACE 27; only those comorbid conditions were separately analyzed, where a minimum of 50 patients with comorbidity could be included to ensure sufficient data.

Results

Demographics

Characteristics of the patients surgically treated for head and neck cancer can be found in Table 1. Most patients were aged between 50 and 60 years (n=359). Only the stage distribution was not different between age groups. Significant differences by age group were found between the 5 age groups in gender, tumor site, surgical treatment, reconstruction type and radiotherapy prior to surgical intervention.

Comorbidity

Distribution of severity of comorbidity over the different age groups is shown in Figure 1. The most prominent difference between the increasing age groups is that patients younger than 50 years mostly (60%) have no comorbidity, and the oldest patients (80 years and over) mostly have mild comorbidity (46%).

Complications

There were slightly more complications in elderly, however no significant differences in the distribution of complications with different severity in the various age groups (Figure 2). In univariate analyses age did not significantly predict complications, although a higher OR was found in the 80+ age group (Table 2). The risk of complications was significantly related to gender, comorbidity, stage, type of surgery, violation of the aero-digestive tract, reconstruction type, neck dissection and length of the intervention. Previous radiotherapy did not predict the occurrence of complications, although only a

Table 1. Characteristics of included surgical interventions

Age group		Total	49 years and younger	Aged 50-60 years	Aged 60-70 years	Aged 70-80 years	Aged 80 and over	P-value (age groups)
Number		1201	205	359	341	214	82	
Sex (%)								
	Male	750 (62)	131 (64)	226 (63)	228 (67)	132 (62)	33 (40)	0.000
	Female	451 (38)	74 (36)	133 (37)	113 (33)	82 (38)	49 (60)	
Stage (%)								
	Stage I	245 (20)	39 (19)	78 (22)	71 (21)	41 (19)	16 (20)	
	Stage II	201 (17)	28 (14)	44 (12)	66 (19)	41 (19)	22 (27)	0.220
	Stage III	170 (14)	29 (14)	55 (15)	48 (14)	30 (14)	8 (10)	
	Stage IV	520 (43)	82 (40)	171 (48)	142 (41)	92 (43)	33 (40)	
	Unknown	65 (5)	27 (13)	11 (3)	14 (4)	10 (5)	3 (4)	
Site (%)								
	Lip and oral cavity	665 (55)	95 (46)	202 (56)	186 (55)	132 (62)	50 (61)	
	Oropharynx	132 (11)	27 (13)	44 (12)	47 (14)	10 (5)	4 (5)	
	Hypopharynx	49 (4)	7 (3)	17 (5)	12 (4)	11 (5)	2 (2)	
	Larynx	128 (11)	11 (5)	46 (13)	42 (12)	22 (10)	7 (9)	0.000
	Nasal cavity and paranasal sinuses	87 (7)	21 (10)	19 (5)	24 (7)	19 (9)	4 (5)	
	Major salivary glands	106 (9)	33 (16)	23 (6)	19 (6)	17 (8)	14 (17)	
	Other	34 (3)	10 (5)	8 (2)	11 (3)	3 (1)	1 (1)	
Surgical treatment (%)								0.091
	Glossectomy	199 (17)	37 (18)	59 (16)	52 (15)	33 (15)	18 (22)	
	Mandibulectomy	254 (21)	32 (16)	81 (23)	76 (22)	51 (24)	14 (17)	
	Total laryngectomy	156 (13)	16 (8)	56 (16)	49 (14)	26 (12)	9 (11)	
	Other surgical treatment:							
	Parotidectomy	89 (7)	25 (12)	20 (6)	15 (4)	17 (8)	12 (15)	
	Sinonasal surgery	58 (5)	10 (5)	11 (3)	18 (5)	15 (7)	4 (5)	
	Tumor resection	223 (19)	34 (17)	67 (19)	71 (21)	36 (17)	15 (18)	
	Maxillectomy	60 (5)	12 (6)	16 (5)	11 (3)	14 (7)	7 (9)	
	Skullbase surgery	16 (1)	8 (4)	2 (1)	5 (2)	1 (1)	0 (0)	
	Ear surgery	14 (1)	3 (2)	4 (1)	5 (2)	2 (1)	0 (0)	
	Primary neck dissection	132 (11)	28 (14)	43 (12)	39 (11)	19 (9)	3 (4)	
	Total number of neck dissections	825 (69)	132 (64)	268 (75)	235 (69)	141 (66)	49 (60)	0.021
Surgery violating ADT (%)								
	No violation ADT	414 (35)	101 (49)	102 (28)	106 (31)	77 (36)	28 (34)	0.000
	Violation ADT	787 (66)	104 (51)	257 (72)	235 (69)	137 (64)	54 (66)	
Reconstruction (%)								
	Primary closure	881 (73)	160 (78)	252 (70)	237 (70)	161 (75)	71 (87)	0.004
	Vascularized flap	118 (10)	13 (6)	43 (12)	31 (9)	23 (11)	8 (10)	
	Free vascularized flap	202 (17)	32 (16)	64 (18)	73 (21)	30 (14)	3 (4)	
Previous radiotherapy (%)		77 (6)	16 (8)	28 (8)	13 (4)	19 (9)	1 (1)	0.021
ACE-27:	Cardiovascular	375 (31)	14 (7)	88 (25)	129 (38)	101 (47)	43 (52)	0.000
	Respiratory	108 (9)	11 (5)	21 (6)	31 (9)	33 (15)	12 (15)	0.000
	Gastro-intestinal	50 (4)	5 (2)	21 (6)	16 (5)	5 (2)	3 (4)	0.187
	Endocrine	94 (8)	5 (2)	21 (6)	32 (9)	22 (10)	14 (17)	0.000
	Neurological	71 (6)	2 (1)	20 (6)	22 (7)	16 (8)	11 (13)	0.001
	Prior malignancy	169 (14)	12 (6)	45 (13)	54 (16)	38 (18)	20 (24)	0.000
	Substance abuse	203 (17)	46 (22)	85 (24)	51 (15)	19 (9)	2 (2)	0.000
	Renal	8 (1)	4 (2)	1 (0)	1 (0)	1 (1)	1 (1)	0.128
	Psychiatric	9 (1)	2 (2)	5 (1)	1 (0)	1 (1)	0 (0)	0.198
	Rheumatologic	35 (3)	3(2)	9 (3)	11 (3)	8 (4)	4 (5)	0.480

ADT = Aero-digestive tract

small proportion of patients (N=77) had previous radiotherapy.

For multivariate analysis only intervention time was included, since a clear intervariable correlation exists with type of surgery (prolonged surgery for total laryngectomy and mandibulectomy), violation of the aero-digestive tract (prolonged surgery for surgery violating aerodigestive tract), type of reconstruction (prolonged surgery for (free) flap

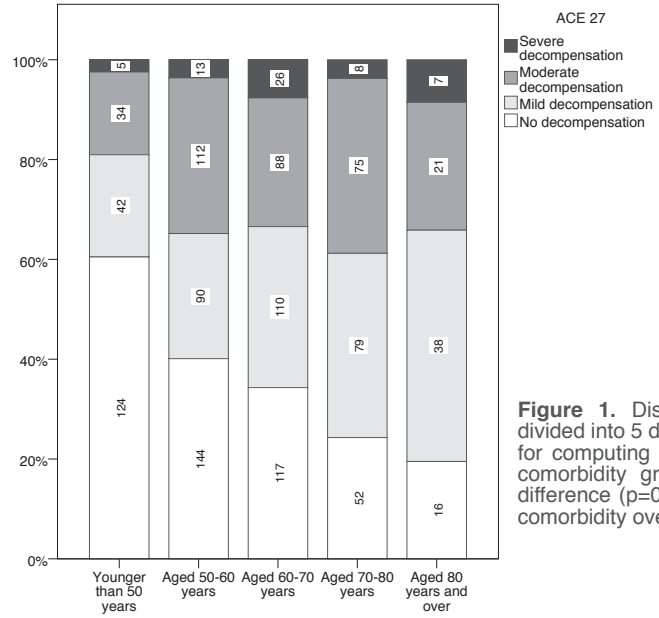

Figure 1. Distribution of comorbidity (ACE 27) divided into 5 different age groups. The denominator for computing the percentage is the total for each comorbidity grade (same fill color). A significant difference (p=0.000) was seen in the distribution of comorbidity over the different age groups.

reconstruction) and neck dissection. In multivariate analysis the risk of complications was twice as high for those 80 years or older (Table 3). Other variables that were associated with the risk of complications were stage, length of surgery, endocrine comorbidity, neurologic comorbidity, previous malignancy and substance abuse. Age was only associated with the risk of cardiopulmonary/neurologic complications. This was only statistically significant for patients aged 80 years and over (p=0.033). Cardiovascular comorbidity, endocrine comorbidity and prolonged surgery were also significantly related to cardiovascular/neurologic complications. Only the surgery related variables, like stage of the tumor and time of the intervention were significantly associated with surgical complications (fistula, leaks, bleeding and hematoma). All other variables, including age and comorbidity, were not associated with surgical complications. The risk of infection was higher with increasing intervention time, respiratory comorbidity and substance abuse.

Discussion

To our knowledge, this is the largest, retrospective study focusing on relation between specific types of comorbidity and complications in patients treated by major surgery for head and neck cancer. We used internationally accepted, validated and reproducible scoring systems: the ACE-27 for describing comorbidity and the Clavien-Dindo classification for the analysis of postoperative complications. Based on our data, it can be said that surgical complications can be expected after surgery on patients with

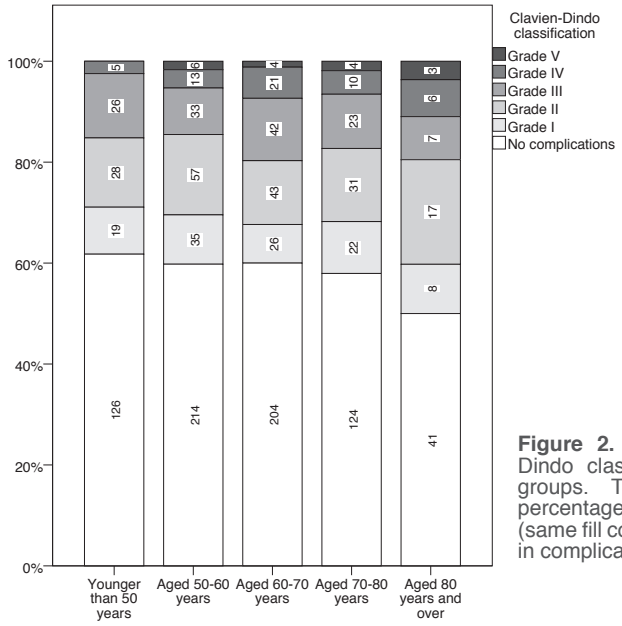

Figure 2. Distribution of complications (Clavien-Dindo classification) divided into 5 different age groups. The denominator for computing the percentage is the total for each complication grade (same fill color). No significant differences were seen in complications between the different age groups.

advanced stage tumors, when prolonged, complex surgery is indicated. Medical, non-surgical complications are linked to elderly patients with a history of cardiovascular- or endocrine disorders.

It is known that elderly cancer patients receive significantly more often a non-standard treatment.(Derks et al., 2005; Sarini et al., 2001) The choice of treatment is frequently based more on prejudices than on facts. The fear of severe postoperative complication in this fragile population leads more often to non-surgical treatment, and in case of operative management extensive surgery is less often performed.(Boje et al., 2013; Datema et al., 2010; Piccirillo et al., 2004; Reid et al., 2001) Moreover poor prognosis of advanced head and neck cancer does not make these patients more attractive for surgery. In order to better assess the occurrence of specific complications, we investigated specific comorbidities in relation to specific complications and whether this differed by age. As expected, and shown by others(Boje et al., 2013) comorbidity increased by age; however, the most aged group in the current study had relatively little comorbidity, since only patients with an operation time of 120 minutes or more were included in the present study. In multivariate analysis, we found advanced age (80+) to be only an independent predictor of cardiopulmonary/neurologic complications. The role of age in the development of postoperative complication less known and the results are controversial.

Table 2. Univariate analysis of different factors influencing the occurrence of complications graded Clavien Dindo II-III-IV-V.

Variable		Odds ratio	P value
Age group	49 years and younger	1 (ref)	0.109
	Aged 50-60 years	1.08 (0.74-1.57)	
	Aged 60-70 years	1.18 (0.81-1.72)	
	Aged 70-80 years	1.15 (0.75-1.74)	
	Aged 80 and over	1.66 (0.97-2.83)	
Gender	**Male**	**1 (ref)**	**0.012**
	Female	**0.72 (0.56-0.93)**	
Comorbidity	**No comorbidity**	**1 (ref)**	**<0.001**
	ACE 27 grade 1 (mild)	**1.74 (1.25-2.40)**	
	ACE 27 grade 2 (moderate)	**3.31 (2.41-4.56)**	
	ACE 27 grade 3 (severe)	**7.46 (4.17-13.35)**	
Stage	**Stage 1**	**1 (ref)**	**<0.001**
	Stage 2	**2.83 (1.76-4.59)**	
	Stage 3	**2.68 (1.63-4.42)**	
	Stage 4	**5.15 (3.42-7.76)**	
Surgery	Other surgical treatment	1 (ref)	
	Glossectomy	1.19 (0.82-1.74)	0.353
	Mandibulectomy	**3.40 (2.49-4.66)**	**<0.001**
	Total laryngectomy	**3.09 (2.13-4.47)**	**<0.001**
Surgery violating ADT	**No violation ADT**	**1 (ref)**	**<0.001**
	Violation ADT	**2.41 (1.82-3.19)**	
Reconstruction	Primary closure	1 (ref)	
	Vascularised flap	**4.07 (2.76-6.02)**	**<0.001**
	Free vascularised flap	**5.22 (3.79-7.20)**	**<0.001**
Neck dissection	**No neck dissection**	**1 (ref)**	**<0.001**
	Neck dissention	**2.29 (1.72-3.06)**	
Length of intervention (25-50-75 percentiles)	**120-200 minutes**	**1 (ref)**	**<0.001**
	200-315 minutes	**1.72 (1.12-2.66)**	
	315-515 minutes	**3.00 (1.98-4.52)**	
	515 minutes and over	**8.94 (5.96-13.41)**	
Previous radiotherapy	No previous radiotherapy		
	Previous radiotherapy	1.33 (0.83-2.15)	0.241

ADT = Aero-digestive tract

In the present study gender, comorbidity, tumor stage, type of surgery, type of reconstruction, neck dissection and the length of surgery, violation of the aero-digestive tract, but not age were associated with postoperative complications in univariate analysis. Just like the present analysis, our previous study showed no prognostic value of age in treatment related complication of oro- and hypopharyngeal cancer patients, and tumor stage was a significant predictor. In that study comorbidity was not a predictor for complications either.(Peters et al., 2011) Another study on laryngeal cancer patients found similar results; only tumor stage was predictive for post-treatment complication, comorbid condition and age were not.(Peters, van der Laan et al., 2011) An earlier study on pharyngeal cancer patients treated by major surgery with free flap reconstruction found comorbidity highly predictive for complication. On the other hand age was not a

Table 3. Multivariate logistic regression analysis of complications Clavien Dindo (CDC) grade II or higher and subdivided into: cardiopulmonary/neurologic complications, fistula/leaks/bleeding/hematoma and infection (local and distant). Factors, which were significant in univariate analysis were included, complemented with the age groups. Comorbidity (ACE 27) was included as type and as based severity.

	All complications (CDC ≥ II)		*Cardiopulmonary/neurologic complications (CDC ≥ II)*		*Fistula, leaks, bleeding and hematoma (CDC ≥ II)*		*Infection (local and distant) (CDC ≥ II)*	
Variable	Odds ratio (95% CI)	P (trend) value	Odds ratio (95% CI)	P (trend) value	Odds ratio (95% CI)	P (trend) value	Odds ratio (95% CI)	P (trend) value
49 years and younger	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Aged 50-60 years	**0.89 (0.57-1.40)**	**0.040**	**1.09 (0.48-2.48)**	**0.033**	0.72 (0.41-1.25)	0.459	1.18 (0.63-2.21)	0.888
Aged 60-70 years	**1.00 (0.63-1.59)**		**1.54 (0.68-3.46)**		0.78 (0.44-1.39)		0.78 (0.39-1.55)	
Aged 70-80 years	**1.08 (0.64-1.80)**		**1.22 (0.49-3.05)**		0.66 (0.33-1.29)		1.15 (0.55-2.42)	
Aged 80 and over	**2.06 (1.08-3.94)**		**3.31 (1.21-9.07)**		0.83 (0.34-2.03)		1.17 (0.44-3.01)	
Female gender	0.83 (0.62-1.11)	0.207	0.76 (0.47-1.23)	0.267	1.01 (0.69-1.49)	0.934	1.21 (0.79-1.86)	0.390
Stage 1	**1 (ref)**		1 (ref)		1 (ref)		1 (ref)	
Stage 2	**1.85 (1.10-3.11)**	**0.000**	1.73 (0.75-4.02)	0.534	**1.27 (0.56-2.89)**	**0.004**	1.91 (0.83-4.36)	0.068
Stage 3	**1.34 (0.76-2.33)**		1.21 (0.48-3.03)		**1.81 (0.81-4.02)**		1.06 (0.42-2.66)	
Stage 4	**2.56 (1.61-4.06)**		1.57 (0.72-3.42)		**2.39 (1.18-4.85)**		2.04 (0.97-4.31)	
120-200 minutes	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
200-315 minutes	**1.46 (0.92-2.33)**	**0.000**	**1.64 (0.74-3.61)**	**0.001**	**1.24 (0.59-2.60)**	**0.000**	**1.24 (0.58-2.69)**	**0.001**
315-515 minutes	**2.02 (1.27-3.20)**		**1.37 (0.61-3.09)**		**2.14 (1.07-4.29)**		**2.12 (1.02-4.39)**	
515 minutes and over	**6.08 (3.81-9.69)**		**3.43 (1.58-7.44)**		**5.03 (2.56-9.85)**		**2.88 (1.39-5.99)**	
Cardiovascular comorbidity	1.16 (0.85-1.58)	0.351	**1.77 (1.11-2.81)**	**0.016**	1.47 (0.99-2.19)	0.055	0.93 (0.59-1.48)	0.766
Respiratory comorbidity	1.44 (0.90-2.30)	0.125	1.23 (0.61-2.46)	0.561	0.87 (0.45-1.69)	0.685	**1.87 (1.02-3.41)**	**0.042**
Gastro-intestinal comorbidity	0.92 (0.48-1.77)	0.793	1.18 (0.47-2.96)	0.719	1.02 (0.46-2.24)	0.963	1.13 (0.47-2.69)	0.784
Endocrine comorbidity	**1.77 (1.07-2.92)**	**0.027**	**2.13 (1.12-4.07)**	**0.022**	1.12 (0.58-2.16)	0.748	0.76 (0.31-1.84)	0.541
Neurologic comorbidity	**1.81 (1.06-3.01)**	**0.030**	1.76 (0.88-3.52)	0.112	1.12 (0.57-2.22)	0.736	1.53 (0.76-3.11)	0.238
Previous malignancy	**1.52 (1.04-2.23)**	**0.032**	1.15 (0.63-2.12)	0.647	1.16 (0.70-1.93)	0.567	1.32 (0.75-2.31)	0.334
Substance abuse	**2.01 (1.44-2.92)**	**0.000**	1.69 (0.99-2.89)	0.056	1.41 (0.91-2.18)	0.126	**1.88 (1.16-3.03)**	**0.010**

significant factor either.(Borggreven et al., 2003) Comorbidity and duration of anesthesia were also found to be predictors of major complications in another study on surgically treated head and neck cancer patients.(Ferrier et al., 2005) Some of these studies included surgically and non-surgically treated patients, and usually only one or two tumor sites. Therefore, the patient population is more coherent, but the sample size is much smaller than the present study.

The results of the multivariate analysis were not really surprising. Length of surgery was found to be one of the most important predictor of surgical and non-surgical complications. Most remarkable is the significant increase of chance of complications in surgeries 515 minutes and longer. Ferrier et al. already showed this relation(Ferrier et al., 2005), they found that anesthesia time of more than 6 hours predicted major complication, with an odds ratio of 7.75.

The influence of different comorbidities on certain type of complication has not been extensively studied in the literature so far. There are studies that make the distinction between different types of complications.(Ferrier et al., 2005; Zabrodsky et al., 2004) One of the few studies to publish on different comorbid conditions and complications was the study by Buitelaar et al.(Buitelaar et al., 2006) In agreement with our findings, this study found age as an independent risk factors for cardiovascular complications. Interestingly, cardiovascular disease did not predict postoperative cardiovascular complication in that study and respiratory complication was predicted not only by pulmonary disease but also by previous myocardial infarction and ASA score. Our cardiovascular comorbidity prevalence of 31% was comparable with the prevalence in other studies (27%-65%) (Borggreven et al., 2003; Datema et al., 2010; Paleri, Narayan, & Wight, 2004; Sanabria et al., 2008), differences can be explained by the fact that these studies used other inclusion criteria.

A recent study also analyzed both surgical site infection and pneumonia in elderly patients after major head and neck surgery.(Milet et al., 2010) The results correspond with our outcome; the occurrence of infections was similar in young and elderly patients. As already mentioned, in the present study complications were analyzed according to its treatment. Infections are generally treated by antibiotics, we did not distinguish between wound and other infections (e.g. pneumonia). Our retrospective analysis is much more reliable this way, but on the other hand we lost information. Prolonged surgery and respiratory comorbidity were significant independent predictors of postoperative infections. Very likely, patients with longer surgery suffered more

often from wound infection and patients with respiratory comorbidity got more often postoperative pneumonia.

Only surgically treated patients were included in the present study, which obviously led to a selection bias. In our institution candidates for surgical treatment of head and neck cancer with multiple- or major comorbidity are screened by the appropriate specialist. Furthermore, anesthesiologist, internal medicine, dietetics and in case of elderly patient gerontologist are always involved in the preoperative assessment process. Their recommendations are incorporated in the treatment plan as discussed by our multidisciplinary head and neck cancer team. We do not know what happened to patients who received non-standard treatment, e.g. curative or palliative radiotherapy instead of extensive surgery. We could not analyze the comorbid conditions of this population and we also do not know the reason of excluding these patients from standard treatment. There is a known tendency to perform more careful preoperative selection of patients with advanced age, reflected in the relative small difference in comorbidity among age groups. On the other hand young individuals tend to undergo extensive surgery despite of weak general medical condition. This selection bias can lead to controversial results, such as more severe complications in the younger population, which has been detected in a previous study on laryngeal cancer patients.(Peters, van der Laan et al., 2011) The low percentage of salvage surgery (6%, Table 1) is surprising and possibly also a result of the above mentioned selection bias. The majority of analyzed population suffered from oral cavity and lip cancer (55%) when the primary surgery is usually the first choice of treatment. Primary radiotherapy is indicated usually in advanced laryngeal and hypopharyngeal cancer when organ preservation can be achieved. Only 15 % of the analyzed cases had laryngeal of hypopharyngeal cancer, which explains the low percentage of salvage surgeries. In order to better assess the role of comorbidity in treatment outcome after treatment in head and neck cancer, a multicenter, prospective study is needed, in which comorbidities and reasons for deciding upon or abstaining from surgery are collected.

In conclusion, the present study showed that elderly patients undergoing major surgery for head and neck cancer have more comorbidities than younger counterparts. Despite of this, surgical complication rates did not increase by age. Only cardiopulmonary/ neurologic complications were associated with age. This is the first major study to analyze comorbidities and complications in detail in a surgically treated patient group, based on organ systems. We found higher rates of medical complications in patients with advanced age and pre-existent comorbidities. Advanced tumor stage and

prolonged surgery time were associated with surgical complications. These data further emphasize the importance of thorough preoperative evaluation including the evaluation of specific types of comorbidity in patients undergoing major surgery for head and neck cancer treatment. For a good assessment of the risk of specific complications, head and neck specialists together with anesthesiologist, internal medicine and in case of elderly patient gerontologist can individualize treatment.

General discussion

In western society the number of elderly people is increasing, and will continue to grow in the next years. With this rise, the number of elderly patients with head and neck cancer rises subsequently. Clinicians are often confronted with the question; what is the optimal treatment of elderly patients with head and neck cancer. Should treatment be influenced by age itself, or are there other identifiable factors before treatment to perform a better selection in patients. In the literature no consensus is reached on this topic, most studies suggest that age itself should not be a factor. Evidently, elderly patients have a shortened life expectancy due to their age. Although this factor should be taken into account, the question arises whether disease specific survival is affected. The literature is not consistent on this topic. Therefore we studied elderly patient with head and neck cancer and aimed to reveal possible predictors of complications after treatment and survival.

Laryngeal and pharyngeal cancer

The two common primary sites in head and neck cancer are the larynx and the pharynx. Although firm treatment protocols exist, guidelines let clinicians to chose between different modalities. These treatment options include minor/major surgery, radiotherapy or a combination of them. Chemotherapy has no additional value in elderly, therefore all patients treated by chemotherapy have been excluded from our studies.(J. P. Pignon et al., 2009) Furthermore, consistent with these results and treatment guidelines only a very few elderly patients were treated with curative chemotherapy in the University Medical Center Groningen. In **chapter 2.1** we found that elderly patient with laryngeal carcinoma did not have more treatment related complications than young patients. This is in line with previous studies(Clayman et al., 1998; Gall et al., 1977; McGuirt & Davis, 1995; T. Pignon et al., 1996), however the difference between different treatment modalities is even more striking in our series. Although elderly patients had more complications after a total laryngectomy, younger patients developed more severe complications. The best explanation for this contradiction is a probable better selection of patients in the elderly group.

With regard to patients treated with radiotherapy, only a small percentage of the patients had no complications during or after radiotherapy. The complications after radiotherapy that occurred were mostly mild or moderate (not requiring hospitalization) in both young and elderly patients. We believe that this was the first study comparing complications after treatment with different treatment modalities. For this purpose we created a classification system for complications that is universally applicable for retrospective scoring surgical and radiotherapy complications. This classification is comparable with

the Common Terminology Criteria for Adverse Events (CTCAE) classification, which is a very comprehensive system, but cannot be applied in a retrospectively because of its complexity. Our classification contains less data, but more applicable for retrospective research.

This classification was also used in the study, described in **chapter 2.2,** which analyzed patients with pharyngeal cancer. This study showed similar results regarding differences between young and elderly pharyngeal cancer patients. Interestingly, comorbidity did not either predict complications; a possible confounder is the large number of young patient with present or past alcohol abuse which resulted in a relative high number of patients with comorbidity. In this chapter not only curative treated patient were analyzed, reasons for choosing a palliative treatment were also analyzed. In younger patient tumor specifics were the most important reason for choosing palliative treatment. This is in line with previous studies(Derks et al., 2005; Yellen et al., 1994) and emphasized the importance of contemplation with elderly patients regarding expectation and possible outcomes of treatment.

Uncommon sites of head and neck cancer

In **chapter 3** we reviewed uncommon malignant tumors of the head and neck, in which the cornerstone of the treatment is surgery. With an incidence of 11 (sinonasal) and 13 (major salivary glands) per 1.000.000 inhabitants(Van Dijk et al., 2012), no large studies exist reviewing complications after treatment especially in elderly patients. Although rare, clinicians regularly face the dilemma, whether elderly patients can cope with major surgery of these malignancies. In both studies, regarding malignant salivary gland tumors and sinonasal tumors, we concluded that age alone should not be a reason to treat elderly patient differently. Treatment planning is not only based on expected complications, but also on expected survival. Comparing survival in group of patients with different age is difficult. In both studies we used the disease specific survival (DSS) which seems to be more reliable as it excludes patients that died of other causes than the tumor. Both studies showed no difference in DSS between young and elderly patients, thus treatment outcome is comparable in the two populations. However, overall survival should not be discarded as it is obvious that elderly patient have a worst prognosis compared to young patients. These studies have the disadvantage of limited number of patients and selection bias.

Relation between specific comorbid conditions and complications after major head and neck surgery

In **chapter 5**, analyzing 1201 surgical interventions, we found that specific comorbidities can help to predict specific complications after surgery. This finding can help clinicians to better inform patients, regarding the risks of surgery, and to make a more weighted and individualized decisions. Moreover, this study explored differences between the occurrence of different types of complications in diverse age groups. This study is the largest study in the present literature analyzing different types of specific complications in young and elderly patients head and neck cancer patients. Surgical complication rate was not found to be increased by age. Higher rates of cardiopulmonary/neurologic complications were found in patients with advanced age and pre-existent comorbidities, while surgical complications were associated with advanced tumor stage and prolonged surgery time.

Free flap surgery

Surgical treatment of advanced head and neck malignancies often results in major defect. It does not allow functional and aesthetic rehabilitation without reconstruction with healthy tissue from other parts of the body. An important method to reconstruct large defects is using free vascularized flaps. The vascularisation of both the flap and the recipient sites are important to ensure a proper adaptation of the flap. In **chapter 4** we retrospectively reviewed all patients undergoing free flap reconstruction in our institution. The results showed that there are no differences between young and elderly patients in regard to (surgical) complications and survival. Although some discussion exists on this subject in literature, these findings are in agreement with most studies. (Beausang et al., 2003; Milet et al., 2010; Ozkan et al., 2005; Serletti et al., 2000; Shaari & Urken, 1999; Vaz et al., 2013) The retrospective nature of this study entails that a strict selection was performed preoperatively, which we would recommend.

Interpretations of this thesis

Determining the best treatment for elderly head and neck cancer patients is though. In the current practice treatment decisions are more often based on prejudices than on evidences.(Derks et al., 2005; Yellen et al., 1994) This thesis provides evidence that, when several physiological and treatment factors are taken into account, elderly patients can physically cope with most treatments. However, providing standard treatment to all elderly patients should not be the conclusion of this thesis, as proper selection is essential before straining curative treatment, regardless of the modality. There are factors, that are major contributors in the decision making process in elderly.

The life expectations of the patients is a factor, not only in terms of survival, but more importantly socially. Most elderly patient have accomplished most of their life goals, and although still living satisfactory, do not feel as if they should pursue additional targets in life. In other words, they do not want to survive by any means, quality of life seems to be more important. All these factors make decision making in elderly more complex, and therefore even more individual approach is necessary to come to the best decision. Although several tools are being developed, personal contact with patients and their families regarding their vision on the best treatment has key importance. In conclusion, it can be said that most elderly patients can physically cope with head and neck cancer treatment, but an individual approach reviewing a patients' beliefs and expectations is crucial.

Confounders in this study

All chapters are based on retrospective data, therefore surely suffering from a bias regarding the choice of treatment in both young and elderly patients. In most of the cases we often do not know the basis for choice of treatment when it was diverging from our treatment protocols. This can result in a selection bias, where fitter and more motivated elderly patients were more often included. Furthermore it is unclear whether more comorbidities, poorer social status, worse cognitive scores or another reason resulted in elderly patients receiving a sub-optimal curative, or non-curative treatment. On the other hand, young patients are easier selected for major surgery or high dose radiotherapy regardless of other factors. This fact can lead to a kind of positive discrimination of young patients, resulting in a relative overtreatment of these patients. In these cases minimal chance of success of the curative treatment, or many/severe comorbidities are disregarded in the decision. Although our research focused on the elderly, this fact is important as the control group consisted of the young population.

Further research

As mentioned earlier, a major confounder is the retrospective nature of our studies. The best option to deny this problem is a prospective study, where beside patient characteristics, diagnostic data, treatment details and outcomes, the reason for the chosen modality are also registered.

Comorbidity remains an important factor that should always be accounted for in outcome of treatment in elderly patients. In this thesis the ACE-27 is used for the classification of comorbidity in head and neck cancer patients. In previous literature regarding comorbidity and head and neck cancer it is also widely used.(Borggreven et

al., 2005; Datema et al., 2010; Ferrier et al., 2005; Piccirillo, 2000; Sanabria et al., 2008) It has the advantage of being more objective compared to the ASA classification(Reid, Alberg, Klassen, Koch, & Samet, 2001), and more comprehensive than the Charlson comorbidity index.(Singh et al., 1997) Therefore, presently the ACE-27 seems to be the most suitable for classification of comorbidity in head and neck cancer, and should be registered in coming research.

In the ACE-27 classification only concurrent physical ailments are scored; however, other domains of functioning decrease as well in elderly. Frailty is a term used to describe the "state of decreased physiological reserves",(Hamaker et al., 2012) though several definitions are known in literature.(Morley, Perry, & Miller, 2002) There are different tools to screen for frail elderly patients before straining treatment. The comprehensive geriatric assessment (CGA) systematically detects diminished resistance in different domains, therefore seems to be more reliable. However it is not widely used, as it is extremely time-consuming.(Extermann & Hurria, 2007; Kenis et al., 2013) Therefore, several screening methods are created to guide experts in the decision making process of head and neck cancer treatment.(Hamaker et al., 2012) Further research possibilities lie within better assessment of (elderly) patients undergoing treatment for head and neck malignancies. Different assessment tools of frailty seem to be promising to gauge treatment outcomes.(Hamaker et al., 2012; Kellen et al., 2010) The Groningen Frailty Index (GFI) is one of these tools analyzing several domains of functioning.(Daniels, van Rossum, Beurskens, van den Heuvel, & de Witte, 2012; Kellen et al., 2010; Metzelthin, van Rossum, de Witte, Hendriks, & Kempen, 2010; Schuurmans et al., 2004) The GFI is a potential tool that improves prediction of treatment outcomes, especially in elderly patient.(Daniels et al., 2012; Pol et al., 2011) Outcome variables used in this thesis are complications and survival after treatment, which are objective measurements of treatment outcome. Treatment outcome can also be defined on a more subjective level, measuring the more general well being after treatment. Quality of life (QOL) is a term describing this well being, and several questionnaires are created to quantify the QOL in patient with head and neck cancer(Aaronson et al., 1993; Bjordal et al., 1994). Although previous studies show that the decline in QOL is equal in young and elderly patient, the baseline QOL is lower in elderly patients.(Derks et al., 2004) It is also known that elderly prefer shorter life with better QOL, than other way around.(Derks et al., 2005; Yellen et al., 1994). Therefore, the influence of several previously mentioned independent variables on the QOL can be interesting.

Recommendations

The choice of treatment of in elderly patients with head and neck malignancies is difficult. This thesis shows that, after a good selection, treatment of elderly patients does not necessarily lead to more complications or poorer disease specific survival. The question how to treat elderly patient therefore should not be directed whether these patients can physically handle the demanding treatment, but rather be based on an individual decision of the doctor and patient. Future studies should be directed at multiple domains of functioning in elderly patients and their effect on treatment outcomes.

Summary

Choices in treatment of elderly patients with head and neck cancer are controversial, physicians face several dilemmas during the treatment of these patients. Comorbidity and age are currently important variables in choosing the right treatment in terms of complications and survival. The Adult Comorbidity Evaluation 27 classification is widely used in this field of research, and is also used in all chapters in this thesis. This thesis provides an overview of these variables in multiple locations of the head and neck, highlighting several clinically important choices in treatment.

Laryngeal cancer is relatively common in elderly patient and the standard treatment is controversial. Therefore in **chapter 2.1** we compared the relationship between co-morbidity and complications in elderly laryngeal cancer patients treated with different modalities. We performed an retrospective analysis of patients 75 years older with laryngeal cancer (n=139) and patients 65 years younger as a reference control group (n=289) diagnosed in our department between 1997 and 2007. Patients between 65 and 75 have been excluded in order to get a clearer view on the effect of age. Analyzing treatment-related complications, we found that co-morbidity rate was more pronounced in the elderly group, but did not result in more complications. Correlation has been found between co-morbidity and complication in the whole patients group, but not in the elderly group. By multivariate analysis, in all age groups radiation therapy (vs. total laryngectomy) and tumor stage were predictors of complications but co-morbidity and age were not. We concluded from these results that there is no reason to treat elderly laryngeal cancer patients differently. However the weaker relation between co-morbidity and complications emphasizes the importance of careful pre-treatment evaluation in elderly.

Although a larger part of oropharyngeal and hypopharyngeal carcinomas is seen in younger patients, the growing population of elderly results in a significant number of patients with these tumor. For radical surgical resection, extensive and mutilating interventions are necessary often with postoperative radiation therapy. Other option is primary radiotherapy which also causes loss of function and consecutively significantly reduced quality of life. The question arises which treatment is best for this population. Consequently **chapter 2.2** was aimed to asses association of co-morbidity, complications and survival in different treatment modalities of pharyngeal cancer patients.

Retrospective analysis was performed of pharyngeal cancer patients, diagnosed between 1997 and 2007 in our institution. Patients 75 years and older (n = 42), were matched with two control patients 64 years and younger (n = 84). Treatment related

complications and survival data were assessed and analyzed. Frequency of co-morbidity was surprisingly similar in both age groups, however discarding alcohol abuse resulted in higher incidence of co-morbidity in the elderly group. Complication rate was not significantly different. In a multivariate analysis only stage found to be a significant predictor of complications. Survival estimates adjusted to sex, age and birth cohort revealed co-morbidity to be a significant predictor for survival in elderly and young patients. We therefore found no evidence to treat elderly pharyngeal cancer patients differently than younger ones, just like in laryngeal cancer patients. Treatment related complications were not predicted by co-morbidities in young and elderly patients; however survival was predicted by comorbidity. Again, we concluded that thorough pre-treatment evaluation and care necessary in the elderly population.

Although malignant sinonasal and major salivary gland tumors are rare, the cornerstone in treatment of these tumors is surgical resection with or without post-operative radiotherapy. Due to the uncommon nature of these tumors in elderly patients, little is known about the treatment outcomes in elderly patients and their possible predictors. In **chapter 3** the emphasize was placed on surgical treatment, therefore complications after treatment were scored with the validated Clavien-Dindo classification system.

Therefore the aim of **chapter 3.1** was to evaluate complications and survival after treatment of sinonasal malignancies, focusing on differences between elderly and younger patients undergoing surgery. This study was conducted by reviewing medical charts of 103 surgically treated patients with sinonasal malignancy (71 under 70 years and 32 aged 70 years and over) in our centre. The results show that although co-morbidity was more common in elderly patients, no significant difference was recorded in complications. In multivariate analysis length of surgery was the only predictor for complication. Furthermore, no significant difference was seen in disease specific survival or recurrence of young and elderly patients. Young patients with malignant epithelial tumors and melanoma had a worse overall survival than patients with other histological subtypes. However, in elderly patients no significant difference was seen in survival between histological subtypes. Based on this study, we concluded that surgery can be also safely performed in elderly sinonasal cancer patients after careful preoperative evaluation and patient selection.

In **chapter 3.2** we focused on another rare localization of head and neck cancer, malignant salivary gland tumors. We aimed to reveal prognostic factors for surgical complications and survival in young and elderly patients with this malignancy. Of the 111

patients, 33 patients were 70 years or older and 78 patients under the 70. Comorbidity and complications were significantly more frequent in elderly patients. However, by multivariate analysis age, comorbidity and length of surgery were not significant independent predictors of complication. Stage was found to be the only independent predictive factor for postoperative complications and disease specific survival. Based on this retrospective study on surgically treated malignant salivary gland tumor patients, age alone should not be a reason to treat elderly patients differently, as it was neither a predictor of complication nor a predictor of disease specific survival.

Surgical treatment of head and neck cancer (HNC) often results in complex defects requiring reconstruction with microvascular free tissue transfer. However, in elderly patients, curative treatment with radical surgery and free flap reconstruction is often withheld. In **chapter 4** the outcomes of free flap surgery in elderly patients is analyzed to see whether this is an feasible technique in elderly patients.

Consequently a retrospective review was conducted of patients that underwent free flap reconstruction following major surgery for HNC between 1995 and 2010. Patients were divided into two age groups: <70 years and ≥70 years. The results show that there were no significant differences between young (n=169) and elderly (n=33) patients in baseline characteristics, including comorbidity, suggesting selection bias in this study. Very likely elderly patients with severe comorbidities were not treated by free flap reconstruction. There were no significant differences between donor and recipient site surgical complications, but significantly more medical complications were seen in young patients. In multivariate analysis, only disease stage was a significant predictor of recipient site complications, and comorbidity was the only significant predictor of medical complications. Furthermore, no significant differences were seen in disease specific survival between young and elderly patients. We concluded biological age, and not chronological age, should be individually determined to assess feasibility of major surgery. Patients should not be denied surgery based on age alone. Optimal patient selection requires thorough pre-operative assessment, including analysis of comorbidities in both young and elderly patients.

Chapters 2 to 4 all analyze a specific subgroup of tumors in the head and neck area based on the primary tumor site. These sub-analyses result in smaller differences between individual tumor types, therefore more reliable outcome. On the other hand analysis of a larger group of patients, including more primary sites can lead to more reliable results, by including other factors and by increasing the sample size. The grade

of comorbidity and complications has been analyzed in the previous chapters, but further specifying these factors (type of comorbidity and sort of complication) could result in more specific predictors and outcomes. Therefore in **chapter 5** we focused on different type of comorbidity and complication in a larger population including different primary sites.

We conducted a retrospective analysis of 1201 major surgical interventions for head and neck malignancies in our center between 1995 and 2010. In univariate analysis comorbidity, stage, mandibulectomy, total laryngectomy, neck dissection and length of surgery significantly predicted grade of complication. Performing multivariate analysis only age, tumor stage, length of surgery and various comorbidities remained significant independent predictors of complication. After specification of the complications, age was only a predictor of medical complications and tumor stage was a significant factor in surgical complications. Length of surgery remained the only significant variable in all types of complications. These data further emphasize the importance of thorough preoperative evaluation of patients undergoing major surgery for head and neck cancer treatment. Age, itself seems not to be a contraindication for major head and neck surgery. We concluded in this chapter that with careful preoperative assessment, risk analysis can be made and physicians can better individualize treatment recommendation.

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Keuze van behandeling bij hoofd-halskanker in oudere patiënten is controversieel. Clinici worden daarbij geconfronteerd met een aantal dilemma's. Comorbiditeit en leeftijd zijn momenteel belangrijke variabelen bij de keuze voor de juiste behandeling. Dit proefschrift geeft een overzicht van deze en andere variabelen die mogelijk van invloed zijn op behandelingsuitkomsten binnen verschillende lokalisaties van hoofd-halskanker.

Het larynxcarcinoom is een van de meest voorkomende kwaadaardige tumoren in het hoofd-halsgebied en komt relatief veel voor bij oudere patiënten. In **hoofdstuk 2.1** werd de relatie geëvalueerd tussen comorbiditeit en complicaties gerelateerd aan de behandeling van oudere patiënten met een larynxcarcinoom.

Hiervoor is van patiënten ouder dan 75 jaar (n=129) en jonger dan 65 jaar (n=283) de medische status geanalyseerd. Alle patiënten zijn gediagnosticeerd met een larynxcarcinoom tussen 1997 en 2007 in het Universitair Medisch Centrum Groningen. Daarbij werd gevonden dat oudere patiënten significant meer comorbiditeit hebben dan jongere patiënten. Echter is er geen significant verschil gevonden in complicaties tussen de leeftijdsgroepen. In jongere patiënten is een significante relatie gevonden tussen comorbiditeit en complicaties. Deze relatie is niet aanwezig bij oudere patiënten. Op basis van deze resultaten werd geconcludeerd dat oudere patiënten op basis van leeftijd niet anders behandeld moeten worden. Andere factoren dan alleen comorbiditeit spelen een rol bij het ontstaan van complicaties in oudere patiënten, dus een nauwkeurige evaluatie is noodzakelijk voor behandeling.

Pharynxcarcinomen komen relatief minder voor bij oudere patiënten, maar keuze van behandeling bij oudere patiënten stelt de clinicus vaak voor een moeilijke beslissing. Daarom richt **hoofdstuk 2.2** zich op het evalueren van de relatie tussen comorbiditeit, complicaties en overleving bij verschillende behandelingsmethoden van pharynxcarcinomen met een nadruk op oudere patiënten.

Hiervoor werd een retrospectieve analyse verricht van pharyngeale kankerpatiënten, gediagnosticeerd in het UMCG tussen 1997 en 2007. Patiënten van 75 jaar en ouder (n=42), werden gekoppeld aan twee patiënten uit de controlegroep van patiënten 64 jaar en jonger (n=84). In dit onderzoek werd gevonden dat comorbiditeit vergelijkbaar was in beide leeftijdsgroepen. Complicaties waren niet significant verschillend tussen leeftijdsgroepen. In de multivariaat analyse werd gevonden dat bij een ernstiger stadium van de ziekte meer complicaties voorkomen. Verder bleek comorbiditeit een significante

voorspeller te zijn van overleving nadat de overleving werd aangepast aan geslacht, leeftijd en geboortecohort.

Ook in dit hoofdstuk werd er geen bewijs gevonden om oudere patiënten met een pharynxcarcinoom anders te behandelen dan jongere patiënten. De aan behandeling gerelateerde complicaties worden niet voorspeld door comorbiditeit bij zowel jonge als oudere patiënten. Echter is comorbiditeit een significante voorspeller van overleving. Daarom is zorgvuldige evaluatie voor de behandeling geïndiceerd bij oudere patiënten. Maligne tumoren van neus(bij)holten en grote speekselklieren zijn zeldzaam, waarbij de kern van de behandeling chirurgisch is, met of zonder aanvullende radiotherapie. Door de zeldzaamheid van deze tumoren is er maar weinig bekend over de behandeluitkomsten (met name in oudere patiënten) en hun mogelijke voorspellers. De nadruk in hoofdstuk 3 ligt op chirurgische complicaties.

In **hoofdstuk 3.1** wordt een onderzoek uitgevoerd naar behandeluitkomsten van maligne sinonasale tumoren, waarbij de focus ligt op verschillen tussen jongeren en oudere patiënten.

Hiervoor werden patiënten met een sinonasale maligniteit (n=107) die chirurgisch zijn behandeld tussen 1995 en 2010 in het UMCG retrospectief geanalyseerd. Patiënten werden verdeeld in patiënten van 70 jaar en ouder (n=34) en 69 jaar en jonger (n=73). Hieruit bleek dat de aanwezigheid van comorbiditeit groter was bij oudere patiënten, echter werd er geen verschil gezien in het ontstaan van complicaties na behandeling. Bij multiple logistische regressie was alleen lengte van de chirurgie een voorspellende factor voor meer complicaties. Tevens werd geen verschil gezien in overleving en recidieven bij jongere en oudere patiënten. Jongere patiënten hadden een slechtere overleving als een plaveiselcelcarcinoom of melanoom werd gevonden. Dit verschil tussen histologische subtypen werd niet gevonden bij oudere patiënten.
De conclusie van deze studie was dat er geen verschil gevonden werd in complicaties, overleving en recidieven tussen oudere en jongere patiënten. Daarom is er geen reden gevonden om oudere patiënten met een sinonasale maligniteit niet volgens protocol te behandelen.

In **hoofdstuk 3.2** werd een andere zeldzame lokalisatie onderzocht van maligne tumoren in het hoofd-halsgebied, te weten de grote speekselklieren. Ook hier wordt de vraag gesteld of er prognostische variabelen aan te wijzen zijn voor het ontstaan van complicaties en overleving, waarbij de nadruk wordt gelegd op verschillen tussen

oudere en jongere patiënten.

Van de 111 onderzochte patiënten waren 33 patiënten 70 jaar of ouder en 78 patiënten jonger dan 70 jaar. Comorbiditeit en complicaties waren significant meer aanwezig in oudere patiënten. Bij multivariate analyse bleken echter leeftijd, comorbiditeit en lengte van chirurgie geen onafhankelijke voorspellers van complicaties. Stadium van de ziekte was de enige onafhankelijke voorspeller van zowel complicaties als ziekte specifieke overleving. Hieruit volgde de conclusie dat leeftijd alléén geen reden is om oudere patiënten anders te behandelen.

Chirurgische resectie van hoofd-halskanker kan leiden tot complexe defecten. Microchirurgische reconstructie met een vrije gevascularisseerde lap is vaak geïndiceerd om een optimaal functioneel en esthetisch resultaat te behalen. De leeftijd van een patiënt zou geen contra-indicatie moeten zijn voor vrije lap chirurgie, echter worden oudere patiënten minder vaak behandeld volgens protocol. Het doel van **hoofdstuk 4** is om de uitkomsten van vrije lap interventies bij hoofd-halskanker patiënten te analyseren aan de hand van een gestandaardiseerde classificatie voor chirurgische complicaties en verschillen te onderzoeken tussen jongere en oudere patiënten.

Patiënten met hoofd-halskanker die in de periode 1995-2010 behandeld zijn met een vrije gevascularisseerde lap in het Universitair Medisch Centrum Groningen werden hiervoor retrospectief geïncludeerd. Er werden in deze groep geen significante verschillen gezien tussen jongere (n=169) en oudere (n=33) patiënten bij de afhankelijke variabelen. Er werden echter bij jongere patiënten significant meer medische complicaties gezien. Bij multivariaat analyse was stadium van de ziekte de enige voorspeller van complicaties gerelateerd aan de ontvangstplaats en comorbiditeit de enige voorspeller van medische complicaties. Leeftijd was geen significante voorspeller bij multivariaat analyse.

Geconcludeerd werd dat in deze groep van oudere patiënten die een vrije lap reconstructie ondergingen, complicaties niet vaker worden gezien, vergeleken met jongere patiënten. Daarom kunnen vrije lappen, bij een goede pre-operatieve selectie van patiënten, bij ouderen net zo succesvol zijn.

In de hoofdstukken 2 tot en met 4 worden specifieke lokalisaties van maligne tumoren in het hoofd-halsgebied onderzocht. Dit resulteert in een meer homogene onderzoeksgroep en daarom ook meer betrouwbare resultaten. Aan de andere kant wordt het mogelijk, door het toevoegen van verschillende lokalisaties aan één studie,

een grotere populatie te creëren. Daarmee kunnen meer betrouwbare uitspraken worden gedaan door toevoeging van meer variabelen. De ernst van de comorbiditeit en complicaties wordt geanalyseerd in alle eerdere hoofdstukken, maar verdere specificatie van deze variabelen (type comorbiditeit en complicaties) zou kunnen leiden tot meer specifieke voorspellers en resultaten. Daarom werd in **hoofdstuk 5** de nadruk gelegd op verschillende type comorbiditeiten in relatie tot verschillende type complicaties met inclusie van verschillende lokalisaties binnen het hoofd-halsgebied.

We hebben daarvoor een retrospectieve analyse gedaan van 1201 patiënten die behandeld werden door middel van uitgebreide chirurgie in verband met hoofd-halskanker in het Universitair Medisch Centrum Groningen tussen 1995 en 2010. Hierbij werden bij univariate analyse verschillende variabelen gevonden die voorspellers waren van ernst van complicaties. Vervolgens waren bij multivariate analyse leeftijd, stadium, lengte van chirurgie en verschillende comorbiditeiten significante voorspellers van complicaties. Bij analyse van specifieke complicaties was leeftijd alleen een voorspeller van internistische complicaties en stadium alleen voor chirurgische complicaties. Lengte van chirurgie bleef de enige voorspeller van alle soorten complicaties. Deze resultaten laten daarmee het belang zien van grondige pre-operatieve evaluatie van patiënt die uitgebreide chirurgie moeten ondergaan in verband met hoofd-halskanker. Leeftijd op zichzelf is echter geen contra-indicaties voor uitgebreide hoofd-halschirurgie. Geconcludeerd werd in dit hoofdstuk dat na grondige pre-operatieve analyse een betere risicoanalyse kan worden gemaakt en dat daarmee een beter individueel advies kan worden gegeven.

De algemene conclusie van dit proefschrift is dat de keuze van behandeling bij ouderen met hoofd-halskanker lastig blijft. Dit manuscript laat zien dat, na een goede selectie, behandeling van oudere patiënten niet hoeft te resulteren in meer complicaties na de behandeling of lagere ziekte specifieke overleving. De vraag hoe oudere patiënten behandeld moeten worden zal dus niet zo zeer gericht moeten worden op de vraag of ze het fysiek aan kunnen, maar meer gericht op een individuele beslissing per patiënt.

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Curriculum Vitae

Thomas Theodoor Adriaan Peters werd op 23 mei 1983 geboren in Nijmegen. In 2002 behaalde Thomas het VWO diploma aan het Stedelijk Lyceum in Zutphen. Na uitgeloot te zijn voor de studie geneeskunde werd in het eerste jaar van zijn studententijd de studie rechtsgeleerdheid gevolgd aan de Rijksuniversiteit Groningen. Na 1 jaar rechtsgeleerdheid is hij ingeloot voor de studie Geneeskunde aan de Rijksuniversiteit Groningen. In het begin van de junior co-schappen in het Universitair Medisch Centrum Groningen werd de interesse in de KNO gewekt en is gestart met een onderzoek onder leiding van dr. G.B. Halmos. In het laatste jaar van zijn studie is Thomas naar Amsterdam verhuisd om daar zijn wetenschappelijke stage te voltooien, waarna hij op 7 juli 2011 het arts-examen behaalde. Na het behalen hiervan werd het gestarte onderzoek onder dr. G.B. Halmos uitgebouwd tot een promotieonderzoek binnen de afdeling KNO-heelkunde in het Universitair Medisch Centrum Groningen. Op 1 juli 2013 is Thomas gestart met de opleiding tot KNO-arts binnen deze afdeling onder leiding van prof. dr. B.F.A.M van der Laan.

Thomas is in 2013 getrouwd met Ianthe Peters-Hartog, en woont samen met haar in Groningen.